Paula Shepard

Access DB#

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Mojdeh Bahar Examiner #: 78209 Date: 02/12/01
Art Unit: 1617 Phone Number 305 1007 Serial Number:
Mail Box and Bldg/Room Location: [illegible] Results Format Preferred (circle): PAPER DISK E-MAIL

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If more than one search is submitted, please prioritize searches in order of need.

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

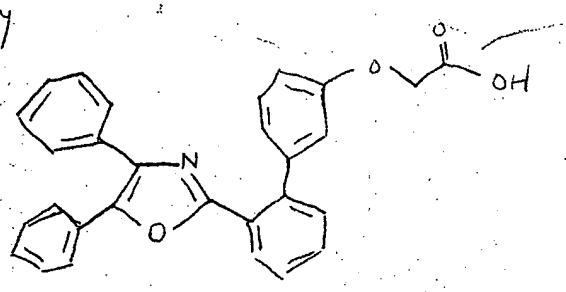
Title of Invention: Method for Treating Diabetes employing an AP2 inhibitor + combination
Inventors (please provide full names): Robl et al

Earliest Priority Filing Date: 09/07/1998

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

Method of treating diabetes using oxazole compounds

+ more specifically



Please see the attached claims 1-11 and 14-15

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Vendors and cost where applicable

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PTO-1590 (1-2000)

=> fil hcaplus

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FILE COVERS 1967 - 16 Feb 2001 VOL 134 ISS 9
FILE LAST UPDATED: 15 Feb 2001 (20010215/ED)

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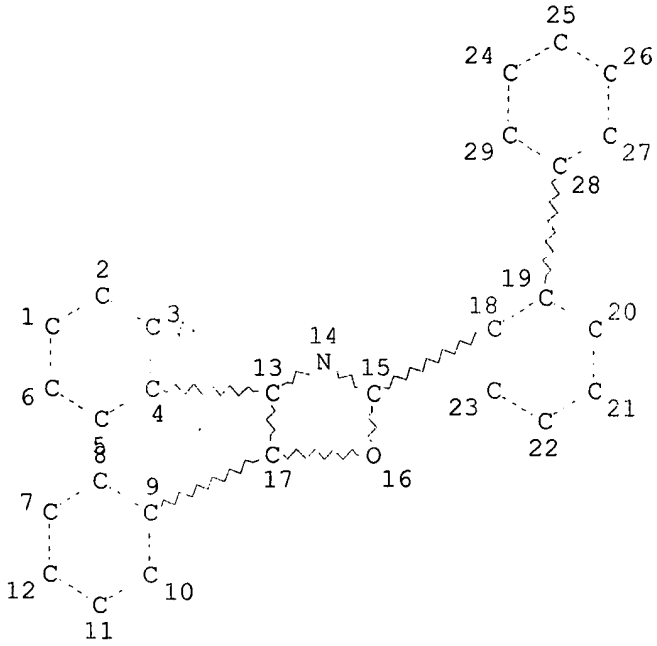
L3 STR



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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS 29

STEREO ATTRIBUTES: NONE
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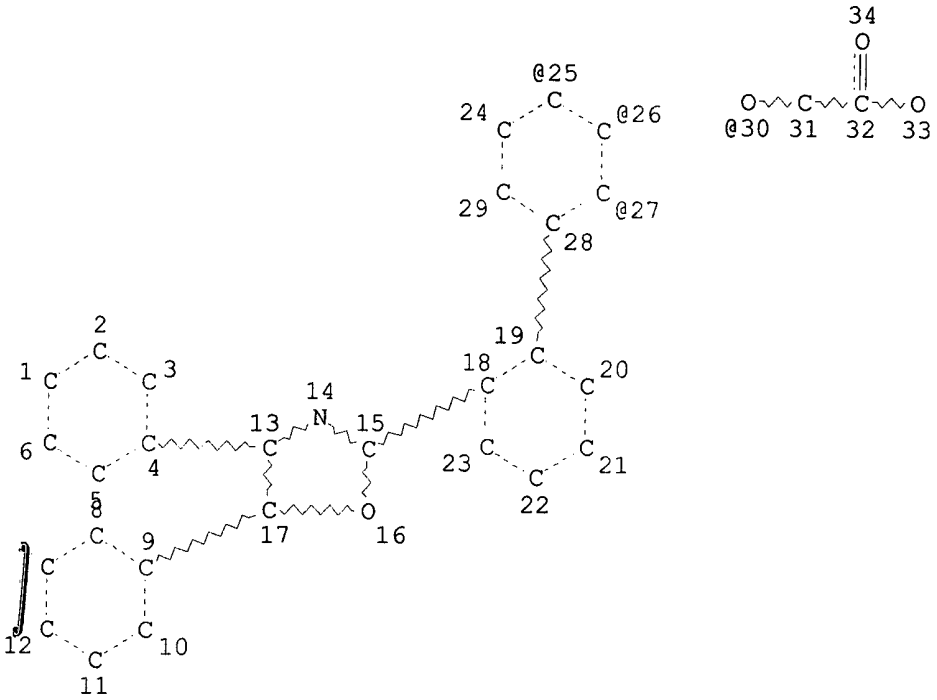
L6 STR



VPA 30-25/26/27 U
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NUMBER OF NODES IS 34

STEREO ATTRIBUTES: NONE
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L8 5 SEA FILE=HCAPLUS ABB=ON PLU=ON L7

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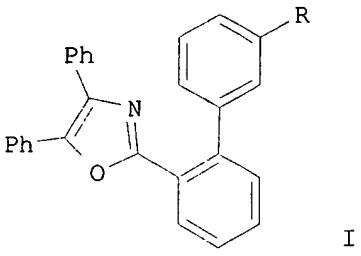
=> d ibib abs hitrn l8 1-5

L8 ANSWER 1 OF 5 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:725467 HCAPLUS
DOCUMENT NUMBER: 133:296436
TITLE: Heterocyclylbiphenyl aP2 inhibitors
INVENTOR(S): Robl, Jeffrey A.; Sulsky, Richard B.; Magnin, David R.
PATENT ASSIGNEE(S): Bristol-Myers Squibb Co., USA
SOURCE: PCT Int. Appl., 206 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2000059506 A1 20001012 WO 2000-US7417 20000320
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 1999-127745 19990405
OTHER SOURCE(S): MARPAT 133:296436
GI



I

AB AP2 inhibiting biphenyls substituted in the 2-position by a substituted 5-membered heterocycle and in the 3'-position by a carboxyalkyl, carboxyalkenyl, carboxymethoxy, carboxymethylamino, or 5-tetrazolylmethyl group, were prepd. The compds. are useful for treating diabetes and related diseases, esp. Type II diabetes (no data) and may be used in combination with another antidiabetic agent such as metformin, glyburide, troglitazone and/or insulin. Thus, 2-BrC6H4CO2H was treated with benzoin and the resulting keto ester cyclized to give 2-(2-bromophenyl)-4,5-diphenyloxazole which was coupled with 3-OCHC6H4B(OH)2 to give the biphenyl deriv. I [R = CHO]. Redn. of the formyl group, chlorination, and reaction with NaCN gave I [R = CH2CN] which was cyclized with Me3SnN3 to give I [R = 5-tetrazoylmethyl].

IT **300657-67-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of heterocyclylbiphenyl derivs. as aP2 inhibitors)

IT **300656-43-3P 300656-54-6P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of heterocyclylbiphenyl derivs. as aP2 inhibitors)

REFERENCE COUNT: 3
REFERENCE(S): (1) Anthony; US 6080870 2000 HCAPLUS
(2) Corbier; US 5811445 A 1998 HCAPLUS
(3) Mjalli; US 5756527 A 1998 HCAPLUS

L8 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:190929 HCAPLUS
DOCUMENT NUMBER: 132:231970
TITLE: Method for treating atherosclerosis employing an aP2 inhibitor, and pharmaceutical combinations with other agents
INVENTOR(S): Robl, Jeffrey A.; Parker, Rex A.; Biller, Scott A.; Jamil, Haris; Jacobson, Bruce L.; Kodukula, Krishna
PATENT ASSIGNEE(S): Bristol-Myers Squibb Co., USA
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000015230	A1	20000323	WO 1999-US21069	19990913
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9961437	A1	20000403	AU 1999-61437	19990913
PRIORITY APPLN. INFO.:			US 1998-100677	19980917
			WO 1999-US21069	19990913

OTHER SOURCE(S): MARPAT 132:231970

AB A method is provided for treating atherosclerosis and related diseases, employing an aP2 inhibitor or a combination of an aP2 inhibitor and another antiatherosclerotic agent, e.g. an HMG CoA reductase inhibitor such as pravastatin.

IT **152575-74-1**

RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aP2 inhibitor for treating atherosclerosis, and combinations with other agents)

REFERENCE COUNT: 2

REFERENCE(S): (1) Failli; US 5218124 A 1993 HCAPLUS
(2) Hotmisligil, G; Science 1996, V274(5291), P1377

L8 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:190928 HCAPLUS

DOCUMENT NUMBER: 132:231969

TITLE: Method for treating diabetes employing an aP2 inhibitor and combination

INVENTOR(S): Robl, Jeffrey A.; Parker, Rex A.; Biller, Scott A.; Jamil, Haris; Jacobson, Bruce L.; Kodukula, Krishna

PATENT ASSIGNEE(S): Bristol-Myers Squibb Co., USA

SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000015229	A1	20000323	WO 1999-US20946	19990913
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9963877	A1	20000403	AU 1999-63877	19990913
PRIORITY APPLN. INFO.:			US 1998-100677	19980917
			WO 1999-US20946	19990913

OTHER SOURCE(S): MARPAT 132:231969

AB A method is provided for treating diabetes and related diseases, such as insulin resistance, obesity, hyperglycemia, hyperinsulinemia, elevated blood levels of free fatty acids or glycerol, hypertriglyceridemia, and esp. Type II diabetes, employing an adipocyte protein aP2 inhibitor or a combination of an aP2 inhibitor and another antidiabetic agent such as

metformin, glyburide, troglitazone and/or insulin.

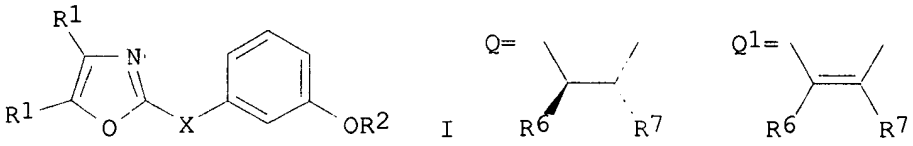
IT **152575-74-1**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aP2 inhibitor and combination with another antidiabetic agent for treatment of diabetes and related diseases)

REFERENCE COUNT: 2
REFERENCE(S): (1) Failli; US 5218124 A 1993 HCAPLUS
(2) Hotmisligil, G; Science (Washington, DC) 1996, V274(5291), P1377 HCAPLUS

L8 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:330768 HCAPLUS
DOCUMENT NUMBER: 122:105867
TITLE: Preparation of (diphenyloxazolyl)oxazoles as platelet aggregation inhibitors
INVENTOR(S): Romine, Jeffrey L.; Meanwell, Nicholas A.
PATENT ASSIGNEE(S): Bristol-Myers Squibb Co., USA
SOURCE: U.S., 21 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5348969	A	19940920	US 1992-862902	19920403

OTHER SOURCE(S): MARPAT 122:105867
GI

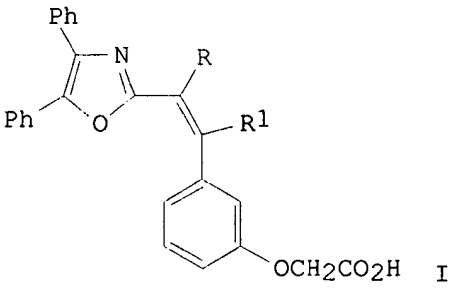


AB Title compds I (X = C6H4, (substituted) heterocyclyl, Q, Q1 wherein R6 = H2N, HOCNH and R7 = H, HO; R1 = Ph, thienyl; R2 = H, R3CH2 wherein R3 = H, MeO, C1-5 alkyl, R4O2C wherein R4 = H, C1-5 alkyl) or pharmaceutically acceptable salt thereof, are prepd. To 4,5-diphenyl-2-oxazolylmethylisocyanide and 3-[(methoxycarbonyl)methoxy]benzaldehyde in THF was added NaH to give I (X = Q (R6 = HOCNH, R7 - HO), R1 = Ph, R2 = MeO2CCH2) (II). In in vitro inhibition of human platelet aggregation the IC50 of II was 0.02 .mu.g/mL.

IT **152575-74-1P 152576-04-0P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of (diphenyloxazolyl)oxazoles as platelet aggregation inhibitors)

L8 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:191585 HCAPLUS
DOCUMENT NUMBER: 120:191585
TITLE: Nonprostanoid prostacyclin mimetics. 5. Structure-activity relationships associated with [3-[4-(4,5-diphenyl-2-oxazolyl)-5-oxazolyl]phenoxy]acetic acid
AUTHOR(S): Meanwell, Nicholas A.; Romine, Jeffrey L.; Rosenfeld, Michael J.; Martin, Scott W.; Trehan, Ashok K.; Wright, J. J. Kim; Malley, Mary F.; Gougoutas, Jack Z.; Brassard, Catherine L.; et al.

CORPORATE SOURCE: Div. Chem., Bristol-Myers Squibb Pharm. Res. Inst., Wallingford, CT, 06492-7660, USA
SOURCE: J. Med. Chem. (1993), 36(24), 3884-903
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB Cis-[3-[2-(4,5-diphenyl-2-oxazolyl)ethenyl]phenoxy]acetic acid (I, R, R1 = H) was previously identified as a nonprostanoid prostacyclin (PGI2) mimetic that potently inhibits ADP-induced aggregation of human platelets with an IC50 of 0.18 .mu.M. As part of an effort to further explore structure-activity relationships for this class of platelet inhibitor and to provide addnl. insight into the nonprostanoid PGI2 mimetic pharmacophore, the effects of constraining the cis-olefin moiety of I (R, R1 = H) into various ring systems was examd. Incorporation of the cis-olefin into I (RR1 = OCH:N, CH:NNH) provided compds. that are equipotent with I (R, R1 = H). However, I (RR1 = N:CHO) inhibits ADP-induced human platelet aggregation in vitro with an IC50 of 0.027 .mu.M, 6-fold more potent than I (R, R1 = H; RR1 = OCH:N, N:CHO). These results suggest that the central oxazole ring of I (RR1 = N:CHO) is functioning as more than a simple scaffold, providing optimal stereodefinition for interaction with the PGI2 receptor. The nitrogen atom of the central heterocycle of I (RR1 = N:CHO) is postulated to engage in hydrogen-bond formation with a donor moiety in the PGI2 receptor protein, an interaction not available to I (RR1 = OCH:N) due to the markedly different topol. In support of this contention, the crystal structures of I (RR1 = OCH:N, N:CHO) contain strong intermol. H bonds between the carboxylic acid H atom and the N atom of the central oxazole ring. Although I (RR1 = OCH:N, N:CHO) are exact isosteres and could, in principle, adopt the same mol. packing arrangement in the solid state, this is not the case, and the intermol. hydrogen-bonding interactions in I (RR1 = OCH:N, N:CHO) are accommodated by entirely different mol. packing arrangements. Incorporation of the olefin moiety of I (R, R1 = H) into a benzene ring provided I (RR1 = CH:CHCH:CH), >60-fold weaker with an IC50 of 11.1 .mu.M. The affinities of I (RR1 = N:CHO, OCH:N, CH:NNMe, CH:CHCH:CH) for the human platelet PGI2 receptor, detd. by displacement of [3H]iloprost, correlated with inhibition of platelet function. The solid-state structures of these compds. were detd. and revealed that the more potent compds. I (RR1 = N:CHO, OCH:N) adopt a relatively planar overall topog. In contrast, the central Ph ring and the phenoxy ring of the weakly active compd. I (RR1 = CH:CHCH:CH) are distorted by 53.degree. from planarity. The chem. shifts of the protons of the phenoxy rings of I suggest that in soln. I (R, R1 = H; RR1 = N:CHO, OCH:N, N:CMeO) adopt a planar conformation while I (RR1 = CH:CHCH:CH) does not. Taken together, these data suggest that the more potent nonprostanoid PGI2 mimetics are those in which elements of the side chain are able to adopt a relatively planar topog. arrangement.

IT **152576-04-0P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(intermediate in prepn. of diphenyloxazolyloxazolylphenoxyacetate prostacyclin mimetic)

IT **152575-74-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as prostacyclin mimetic)

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FILE LAST UPDATED: 01 May 1997 (19970501/UP)

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DICTIONARY FILE UPDATES: 15 FEB 2001 HIGHEST RN 321895-78-7

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L7 ANSWER 1 OF 5 REGISTRY COPYRIGHT 2001 ACS
RN 300657-67-4 REGISTRY
CN Acetic acid, [[2'-(4,5-diphenyl-2-oxazolyl)-6'-methyl[1,1'-biphenyl]-3-yl]oxy]-, ethyl ester (9CI) (CA INDEX NAME)

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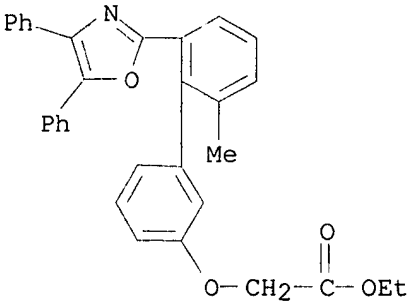
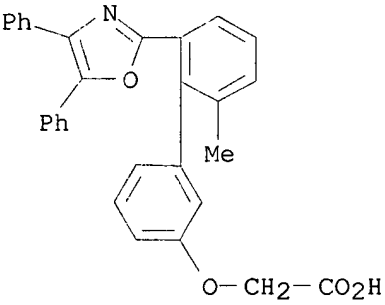
MF C32 H27 N O4
SR CA
LC STN Files: CA, CAPLUS



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:296436

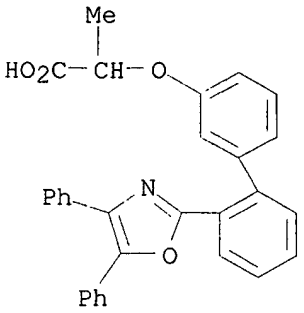
L7 ANSWER 2 OF 5 REGISTRY COPYRIGHT 2001 ACS
RN 300656-54-6 REGISTRY
CN Acetic acid, [[2'-(4,5-diphenyl-2-oxazolyl)-6'-methyl[1,1'-biphenyl]-3-yl]oxy]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C30 H23 N O4
SR CA
LC STN Files: CA, CAPLUS



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:296436

L7 ANSWER 3 OF 5 REGISTRY COPYRIGHT 2001 ACS
RN 300656-43-3 REGISTRY
CN Propanoic acid, 2-[[2'-(4,5-diphenyl-2-oxazolyl)[1,1'-biphenyl]-3-yl]oxy]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C30 H23 N O4
SR CA
LC STN Files: CA, CAPLUS



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:296436

L7 ANSWER 4 OF 5 REGISTRY COPYRIGHT 2001 ACS
RN 152576-04-0 REGISTRY
CN Acetic acid, [[2'-(4,5-diphenyl-2-oxazolyl)[1,1'-biphenyl]-3-yl]oxy]-, methyl ester (9CI) (CA INDEX NAME)
MF C30 H23 N O4
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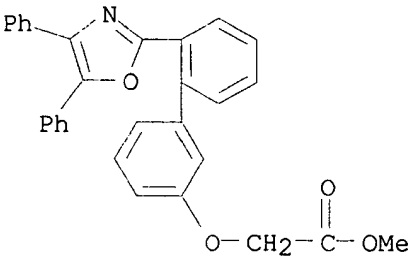
LC STN Files: CA, CAPLUS, USPATFULL



2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 122:105867

REFERENCE 2: 120:191585

L7 ANSWER 5 OF 5 REGISTRY COPYRIGHT 2001 ACS
RN 152575-74-1 REGISTRY
CN Acetic acid, [[2'-(4,5-diphenyl-2-oxazolyl)[1,1'-biphenyl]-3-yl]oxy]- (9CI) (CA INDEX NAME)
MF C29 H21 N O4
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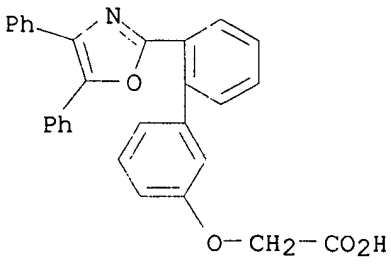

4 REFERENCES IN FILE CA (1967 TO DATE)
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REFERENCE 1: 132:231970

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REFERENCE 4: 120:191585

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This file contains CAS Registry Numbers for easy and accurate substance identification.

This file supports REGlstRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

Now you can extend your author, patent assignee, patent information, and title searches back to 1907. The records from 1907-1966 now have this searchable data in CAOLD. You now have electronic access to all of CA: 1907 to 1966 in CAOLD and 1967 to the present in HCAPLUS on STN.

=>

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=> d stat que l11 nos

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L3              STR
L5           54 SEA FILE=REGISTRY SSS FUL L3
L6              STR
L7            5 SEA FILE=REGISTRY SUB=L5 SSS FUL L6
L8            5 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7
L10          49 SEA FILE=REGISTRY ABB=ON  PLU=ON  L5 NOT L7
L11           1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L10 NOT L8
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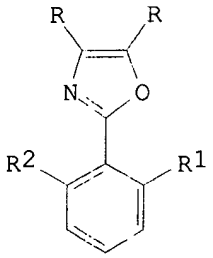
=>

=>

=> d ibib abs hitrn l11 1

L11 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1987:636570 HCAPLUS
DOCUMENT NUMBER: 107:236570
TITLE: Oxazoles are masked carboxyls that activate ortho-leaving groups in nucleophilic aromatic substitution
AUTHOR(S): Cram, Donald J.; Bryant, Judi A.; Doxsee, Kenneth M.
CORPORATE SOURCE: Dep. Chem. Biochem., Univ. California, Los Angeles, CA, 90024, USA
SOURCE: Chem. Lett. (1987), (1), 19-22
CODEN: CMLTAG; ISSN: 0366-7022
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 107:236570
GI



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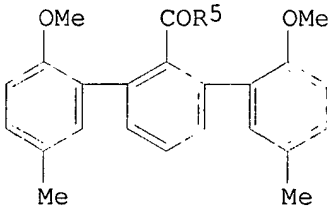

II

AB Oxazoles I (R = Ph, Me; R1 = H, R2 = F, OMe; R1 = R2 = F) reacted with R3C6H4MgBr (R3 = 2-OMe, 4-OMe) or 2,5(OMe)MeC6H3Li to give substituted biphenyl or terphenyl products. The oxazole groups were subsequently converted to esters, acids, or amides to give biphenyl acids or derivs., e.g., 2-MeOC6H4C6H4CO2R4-2 (R4 = H, Me) and terphenyl acid derivs. II (R5 = OMe, NH2). These reactions provide a new unsym. aryl-aryl coupling reaction.

IT **111603-43-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and decompn. of, biphenylcarboxylic acid deriv. from)

IT **111603-52-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and decompn. of, terphenylcarboxylate from)

IT **111603-45-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

=>

=>

=> fil reg

FILE 'REGISTRY' ENTERED AT 19:15:35 ON 16 FEB 2001
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

STRUCTURE FILE UPDATES: 15 FEB 2001 HIGHEST RN 321895-78-7
DICTIONARY FILE UPDATES: 15 FEB 2001 HIGHEST RN 321895-78-7

TSCA INFORMATION NOW CURRENT THROUGH July 8, 2000

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Structure search limits have been increased. See HELP SLIMIT for details.

=>

=>

=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 19:15:42 ON 16 FEB 2001
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1967 - 16 Feb 2001 VOL 134 ISS 9
FILE LAST UPDATED: 15 Feb 2001 (20010215/ED)

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=>

=> select hit rn l11 1

E31 THROUGH E33 ASSIGNED

=> fil reg

FILE 'REGISTRY' ENTERED AT 19:15:57 ON 16 FEB 2001
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

STRUCTURE FILE UPDATES: 15 FEB 2001 HIGHEST RN 321895-78-7
DICTIONARY FILE UPDATES: 15 FEB 2001 HIGHEST RN 321895-78-7

TSCA INFORMATION NOW CURRENT THROUGH July 8, 2000

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Structure search limits have been increased. See HELP SLIMIT for details.

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=> s e31-e33

             1 111603-43-1/BI
               (111603-43-1/RN)
             1 111603-45-3/BI
               (111603-45-3/RN)
             1 111603-52-2/BI
               (111603-52-2/RN)
L12          3 (111603-43-1/BI OR 111603-45-3/BI OR 111603-52-2/BI)

=>

=>

=> d ide can l12 1-3


L12  ANSWER 1 OF 3  REGISTRY  COPYRIGHT 2001 ACS
RN   111603-52-2  REGISTRY
CN   Oxazole, 2-(2,2''-dimethoxy-5,5''-dimethyl[1,1':3',1''-terphenyl]-2'-yl)-
     4,5-diphenyl- (9CI)  (CA INDEX NAME)
FS   3D CONCORD
MF   C37 H31 N O3
SR   CA
LC   STN Files:   BEILSTEIN*, CA, CAPLUS, CASREACT
         (*File contains numerically searchable property data)
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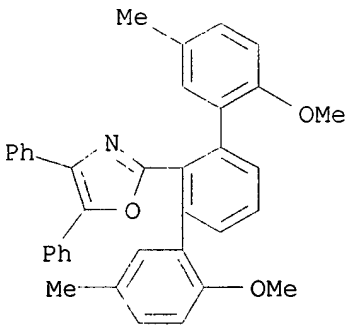


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               1 REFERENCES IN FILE CA (1967 TO DATE)
               1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE   1:  107:236570

L12  ANSWER 2 OF 3  REGISTRY  COPYRIGHT 2001 ACS
RN   111603-45-3  REGISTRY
CN   Oxazole, 2-(4'-methoxy[1,1'-biphenyl]-2-yl)-4,5-diphenyl- (9CI)  (CA INDEX
     NAME)
FS   3D CONCORD
MF   C28 H21 N O2
SR   CA
LC   STN Files:   BEILSTEIN*, CA, CAPLUS, CASREACT
         (*File contains numerically searchable property data)
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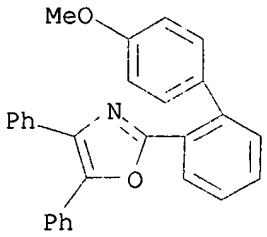
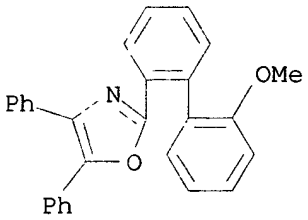


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 107:236570

L12 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2001 ACS
RN **111603-43-1** REGISTRY
CN Oxazole, 2-(2'-methoxy[1,1'-biphenyl]-2-yl)-4,5-diphenyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C28 H21 N O2
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT
(*File contains numerically searchable property data)



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 107:236570

=> d stat que l18 nos

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L5           54 SEA FILE=REGISTRY SSS FUL L3
L6              STR
L7            5 SEA FILE=REGISTRY SUB=L5 SSS FUL L6
L8            5 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7
L10          49 SEA FILE=REGISTRY ABB=ON  PLU=ON  L5 NOT L7
L11           1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L10 NOT L8
L13       13312 SEA FILE=REGISTRY ABB=ON  PLU=ON  OXAZOLE?/CN
L14         173 SEA FILE=REGISTRY ABB=ON  PLU=ON  AP2?
L15       31521 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L13 OR ?OXAZOLE?
L16        2486 SEA FILE=HCAPLUS ABB=ON  PLU=ON  AP2? OR AP(W)2 OR L14
L17           3 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L16 AND L15
L18           1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L17 NOT (L8 OR L11)
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=> d ibib abs hitrn l18 1

L18 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:768008 HCAPLUS
DOCUMENT NUMBER: 132:73932

TITLE: Dynamin-dependent endocytosis of ionotropic glutamate receptors
AUTHOR(S): Carroll, Reed C.; Beattie, Eric C.; Xia, Houhui; Luscher, Christian; Altschuler, Yoram; Nicoll, Roger A.; Malenka, Robert C.; Von Zastrow, Mark
CORPORATE SOURCE: Departments of Psychiatry, University of California, San Francisco, CA, 94143, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1999), 96(24), 14112-14117
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Little is known about the mechanisms that regulate the no. of ionotropic glutamate receptors present at excitatory synapses. Herein, we show that GluR1-contg. .alpha.-amino-3-hydroxy-5-methyl-4-**isoxazolepropionic** acid (AMPA) receptors (AMPARs) are removed from the postsynaptic plasma membrane of cultured hippocampal neurons by rapid, ligand-induced endocytosis. Although endocytosis of AMPARs can be induced by high concns. of AMPA without concomitant activation of NMDA receptors (NMDARs), NMDAR activation is required for detectable endocytosis induced by synaptically released glutamate. Activated AMPARs colocalize with **AP2**, a marker of endocytic coated pits, and endocytosis of AMPARs is blocked by biochem. inhibition of clathrin-coated pit function or overexpression of a dominant-neg. mutant form of dynamin. These results establish that ionotropic receptors are regulated by dynamin-dependent endocytosis and suggest an important role of endocytic membrane trafficking in the postsynaptic modulation of neurotransmission.
REFERENCE COUNT: 33
REFERENCE(S): (1) Altschuler, Y; J Cell Biol 1998, V143, P1871 HCAPLUS
(2) Betz, W; Annu Rev Physiol 1998, V60, P347 HCAPLUS
(3) Carroll, R; Nat Neurosci 1999, V2, P454 HCAPLUS
(4) Cremona, O; Curr Opin Neurobiol 1997, V7, P323 HCAPLUS
(5) Damke, H; J Cell Biol 1994, V127, P915 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=>

=>

=> d stat que l22 nos

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L3              STR
L5           54 SEA FILE=REGISTRY SSS FUL L3
L6              STR
L7            5 SEA FILE=REGISTRY SUB=L5 SSS FUL L6
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L10          49 SEA FILE=REGISTRY ABB=ON  PLU=ON  L5 NOT L7
L11           1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L10 NOT L8
L13       13312 SEA FILE=REGISTRY ABB=ON  PLU=ON  OXAZOLE?/CN
L14         173 SEA FILE=REGISTRY ABB=ON  PLU=ON  AP2?
L15       31521 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L13 OR ?OXAZOLE?
L16        2486 SEA FILE=HCAPLUS ABB=ON  PLU=ON  AP2? OR AP(W)2 OR L14
L17           3 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L16 AND L15
L18           1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L17 NOT (L8 OR L11)
L19          98 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L16(L)(?DIABET? OR ?OBES? OR
                 ?HYPERGLYCE? OR ?HYPERINSULIN? OR ?HYPERTRIGLY? OR ?HYPERFATTY?
                  OR ?HYPERGLYCEROL?)
L20         362 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L16(L)(?MEDIC? OR ?PHARM? OR
                 ?DRUG? OR ?THERAP? OR ?TREAT?)
L21          33 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L19 AND L20
L22          30 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L21 NOT (L8 OR L11 OR L18)
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=> d ibib abs hitrn l22 1-30

L22 ANSWER 1 OF 30 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:776282 HCAPLUS
DOCUMENT NUMBER: 134:51258
TITLE: Up-regulation of peroxisome proliferator-activated receptors (PPAR-.alpha.) and PPAR-.gamma. messenger ribonucleic acid expression in the liver in murine obesity: troglitazone induces expression of PPAR-.gamma.-responsive adipose tissue-specific genes in the liver of obese diabetic mice
AUTHOR(S): Memon, Riaz A.; Tecott, Laurence H.; Nonogaki, Katsunori; Beigneux, Anne; Moser, Arthur H.; Grunfeld, Carl; Feingold, Kenneth R.
CORPORATE SOURCE: Metabolism Section, Medical Service, Department of Veterans Affairs Medical Center, San Francisco, CA, 94121, USA
SOURCE: Endocrinology (2000), 141(11), 4021-4031
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Peroxisome proliferator-activated receptors (PPARs) are transcription factors that play an important role in the regulation of genes involved in lipid utilization and storage, lipoprotein metab., adipocyte differentiation, and insulin action. The three isoforms of the PPAR family, i.e. .alpha., .delta., and .gamma., have distinct tissue distribution patterns. PPAR-.alpha. is predominantly present in the liver, and PPAR-.gamma. in adipose tissue, whereas PPAR-.delta. is ubiquitously expressed. A recent study reported increased PPAR-.gamma. mRNA expression in the liver in ob/ob mice; however, it is not known whether increased PPAR-.gamma. expression in the liver has any functional consequences. The expression of PPAR-.alpha. and -.delta. in the liver in **obesity** has not been detd. We have now examd. the mRNA levels of PPAR-.alpha., -.delta., and -.gamma. in three murine models of **obesity**, namely, ob/ob (leptin-deficient), db/db (leptin-receptor deficient), and serotonin 5-HT2c receptor (5-HT2cR) mutant mice. 5-HT2cR mutant mice develop a late-onset **obesity** that is assocd. with higher plasma leptin levels. Our results show that PPAR-.alpha. mRNA levels in the liver are increased by 2- to 3-fold in all three **obese** models, whereas hepatic PPAR-.gamma. mRNA levels are increased by 7- to 9-fold in ob/ob and db/db mice and by 2-fold in **obese** 5-HT2cR mutant mice. PPAR-.delta. mRNA expression is not altered in ob/ob or db/db mice. To det. whether increased PPAR-.gamma. expression in the liver has any functional consequences, we examd. the effect of troglitazone **treatment** on the hepatic mRNA levels of several PPAR-.gamma.-responsive adipose tissue-specific genes that have either no detectable or very low basal expression in the liver. The **treatment** of lean control mice with troglitazone significantly increased the expression of adipocyte fatty acid-binding protein (**aP2**) and fatty acid translocase (FAT/CD36) in the liver. This troglitazone-induced increase in the expression of **aP2** and FAT/CD36 was markedly enhanced in the liver in ob/ob mice. Troglitazone also induced a pronounced increase in the expression of uncoupling protein-2 in the liver in ob/ob mice. In contrast to the liver, troglitazone did not increase the expression of **aP2**, FAT/CD36, and uncoupling protein-2 in adipose tissue in lean or ob/ob mice. Taken together, our results suggest that the effects of PPAR-.gamma. activators on lipid metab. and energy homeostasis in **obesity** and type 2 **diabetes** may be partly mediated through their effects on PPAR-.gamma. in the liver.
REFERENCE COUNT: 40
REFERENCE(S): (1) Abumrad, N; Biochim Biophys Acta 1999, V1441, P4 HCAPLUS

(2) Aitman, T; Nat Genet 1999, V21, P76 HCAPLUS
(3) Aoyama, T; J Biol Chem 1998, V273, P5678 HCAPLUS
(4) Asayama, K; Mol Cell Biochem 1999, V194, P227 HCAPLUS
(5) Auboeuf, D; Diabetes 1997, V46, P1319 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 2 OF 30 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:516364 HCAPLUS
DOCUMENT NUMBER: 134:40647
TITLE: Regulation of leptin by agouti
AUTHOR(S): Claycombe, Kate J.; Xue, Bing Zhong; Mynatt, Randall L.; Zemel, Michael B.; Moustaid-Moussa, Naima
CORPORATE SOURCE: Department of Nutrition, University of Tennessee, Knoxville, TN, 37996, USA
SOURCE: Physiol. Genomics (2000), 2, 101-105
CODEN: PHGEFP; ISSN: 1094-8341
URL: http://physiolgenomics.physiology.org/cgi/reprint/2/3/101.pdf
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Dominant mutations at the mouse Agouti locus lead to ectopic expression of the Agouti gene and exhibit **diabetes**, **obesity**, and yellow coat color. **Obese** yellow mice are **hyperinsulinemic** and hyperleptinemic, and we hypothesized that Agouti directly induces leptin secretion. Accordingly, we used transgenic mice expressing agouti in adipocytes (under the control of a P2 promoter, **aP212**) to examine changes in leptin levels. Agouti expression in adipose tissue did not significantly alter food intake, wt. gain, fat pad wt., or insulinemia; however, the transgenic mice were **hyperglycemic**. We demonstrated that plasma leptin levels are approx. twofold higher in **aP212** transgenic mice compared with their resp. controls, whereas ubiquitous expression of agouti (under the control of .beta.-actin promoter, BAP20) led to a sixfold increase in leptin. Insulin **treatment** of a P212 mice increased adipocyte leptin content without affecting plasma leptin levels. These finding were further confirmed in vitro in 3T3-L1 adipocytes **treated** with recombinant Agouti protein and/or insulin. Agouti but not insulin significantly increased leptin secretion, indicating that insulin enhances leptin synthesis but not secretion while Agouti increases both leptin synthesis and secretion. This increased leptin synthesis and secretion was due to increased leptin mRNA levels by Agouti. Interestingly, agouti regulation of leptin was not mediated by melanocortin receptor 4, previously implicated in agouti regulation of food intake. These results suggest that increased leptin secretion by agouti may serve to limit agouti induced **obesity**, independent of melanocortin receptor antagonism, and indicate that interaction between **obesity** genes may play a key role in **obesity**.
REFERENCE COUNT: 33
REFERENCE(S): (1) Barr, V; Endocrinology 1997, V138, P4463 HCAPLUS
(3) Bultman, S; Proc Natl Acad Sci USA 1991, V88, P8062 HCAPLUS
(5) Chagnon, Y; Mol Med 1997, V3, P663 HCAPLUS
(6) Chessler, S; Diabetes 1998, V47, P239 HCAPLUS
(7) Frederich, R; J Clin Invest 1995, V96, P1658 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 3 OF 30 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:362595 HCAPLUS
DOCUMENT NUMBER: 133:13403
TITLE: Adipocyte containing ob gene promoter for screening modulators useful in treatment of anorexia, obesity, and other diseases
INVENTOR(S): Briggs, Michael R.; Auwerx, Johan; De Vos, Piet;

Staels, Bart; Croston, Glenn E.; Miller, Stephen G.
PATENT ASSIGNEE(S): Ligand Pharmaceuticals Inc., USA
SOURCE: U.S., 64 pp., Cont.-in-part of U.S. Ser. No. 558,588, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6068976	A	20000530	US 1996-618100	19960319
CA 2215387	AA	19960926	CA 1996-2215387	19960319
PRIORITY APPLN. INFO.:			US 1995-408584	19950320
			US 1995-418096	19950405
			US 1995-510584	19950802
			US 1995-558588	19951030
			US 1995-7390	19951121
			US 1995-7721	19951130
			US 1995-8601	19951214

AB This invention relates to the isolation and cloning of the promoter and other control regions of a human ob gene. It provides a method for identifying and screening for agents useful for the treatment of diseases and pathol. conditions affected by the level of expression of an ob gene. These agents interact directly or indirectly with the promoter or other control regions of the ob gene. A PPAR.gamma. agonist, BRL49653, has been identified to be useful in treating anorexia, cachexia, and other diseases characterized by insufficient food intake or body wt. loss. Modulators of ob gene expression may be used to treat other diseases such as obesity, diabetes, hypertension, cardiovascular diseases and infertility.

REFERENCE COUNT: 9
REFERENCE(S):
(1) Anon; EP 0764722 A2 1997 HCAPLUS
(2) Anon; WO 9718228 1997 HCAPLUS
(3) de La Brousse; US 5698389 1997 HCAPLUS
(4) de Vos; J Biol Chem 1995, V270(27), P15958 HCAPLUS
(5) Faisst, S; Nucleic Acids Research 1992, V20(1), P3 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 4 OF 30 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:293709 HCAPLUS
DOCUMENT NUMBER: 133:56396
TITLE: Role of PPAR.delta. in the control of adipogenesis by fatty acids
AUTHOR(S): Bastie, Claire; Luquet, Serge; Jehl-Pietri, Chantal; Grimaldi, Paul A.
CORPORATE SOURCE: Centre de Biochimie, Nice, 06108, Fr.
SOURCE: Biomed. Health Res. (2000), 37(Adipocyte Biology and Hormone Signaling), 41-50
CODEN: BIHREN; ISSN: 0929-6743
PUBLISHER: IOS Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 25 refs. High fat feeding leads in a few weeks to development of **obesity** by increasing the no. and the size of adipocytes. It is now established that nutritional long-chain fatty acids are implicated in these actions on adipose tissue development by a mechanism that remained poorly understood. During the last past years, it has been demonstrated that nuclear receptors of the PPAR subfamily are crucial actors in the control of adipose differentiation. Among them, PPAR.gamma., activated by specific prostanoids, plays a crucial role in the control of adipocyte gene expression and terminal differentiation. PPAR.delta. is activated by long-chain fatty acids and expressed early during adipose differentiation. Despite these observations, its role in the control of adipose tissue mass has remained unclear. To delineate

more precisely this role, we have forced its expression in fibroblasts and investigated the response to fatty acids and other putative PPAR activators on gene expression and adipocyte differentiation. We found that activation of PPAR.delta. by fatty acids led to a rapid induction of genes such as FAT and **aP2** and to a delayed induction of PPAR.gamma. gene but not to terminal differentiation. Typical adipogenesis with expression of the overall differentiation program was obtained when PPAR.delta.-expressing fibroblasts were first **treated** with fatty acids and then exposed to specific PPAR.gamma. activators. Furthermore, we also found that PPAR.delta.-expressing fibroblasts can undergo post-confluent proliferation when exposed to PPAR.delta. agonists. This new phenotype is nearly similar to that of actual preadipocytes such as Ob1771 cells. Taking together, these data strongly suggest that PPAR.delta. plays an important role in the regulation of adipose tissue mass as a nuclear mediator of the fatty acid effects on preadipose cell proliferation and differentiation.

REFERENCE COUNT: 25
REFERENCE(S):
(1) Abumrad, N; J Biol Chem 1993, V268, P17665 HCAPLUS
(2) Ailhaud, G; Annu Rev Nutr 1992, V12, P207 HCAPLUS
(3) Amri, E; J Biol Chem 1995, V270, P2367 HCAPLUS
(4) Amri, E; J Lipid Res 1991, V32, P1449 HCAPLUS
(5) Amri, E; J Lipid Res 1991, V32, P1457 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 5 OF 30 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:293502 HCAPLUS
DOCUMENT NUMBER: 133:84110
TITLE: Fenofibrate and Rosiglitazone Lower Serum Triglycerides with Opposing Effects on Body Weight
AUTHOR(S): Chaput, Evelyne; Saladin, Regis; Silvestre, Martine; Edgar, Alan D.
CORPORATE SOURCE: Department of Metabolic Diseases, Laboratoire Fournier, Daix, 21121, Fr.
SOURCE: Biochem. Biophys. Res. Commun. (2000), 271(2), 445-450
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Activators of peroxisome proliferator activated receptors (PPARs) are effective **drugs** to improve the metabolic abnormalities linking **hypertriglyceridemia** to **diabetes**, **hyperglycemia**, insulin-resistance, and atherosclerosis. We compared the **pharmacol.** profile of a PPAR.alpha. activator, fenofibrate, and a PPAR.gamma. activator, rosiglitazone, on serum parameters, target gene expression, and body wt. gain in (fa/fa) fatty Zucker rats and db/db mice as well as their assocn. in db/db mice. Fenofibrate faithfully modified the expression of PPAR.alpha. responsive genes. Rosiglitazone increased adipose tissue **aP2** mRNA in both models while increasing liver acyl CoA oxidase mRNA in db/db mice but not in fatty Zucker rats. Both **drugs** lowered serum triglycerides yet rosiglitazone markedly increased body wt. gain while fenofibrate decreased body wt. gain in fatty Zucker rats. KRP 297, which has been reported to be a PPAR.alpha. and .gamma. co-activator, also affected serum triglycerides and insulin in fatty Zucker rats although no change in body wt. gain was noted. These results serve to clearly differentiate the metabolic finality of two distinct classes of **drugs**, as well as their corresponding nuclear receptors, having similar effects on serum triglycerides. (c) 2000 Academic Press.

REFERENCE COUNT: 21
REFERENCE(S):
(1) Balfour, J; Drugs 1990, V40, P260 HCAPLUS
(2) Brewer, H; Am J Cardiol 1999, V83, P3F HCAPLUS
(3) Chinetti, G; J Biol Chem 1998, V273, P25573 HCAPLUS
(4) Costet, P; J Biol Chem 1998, V273, P29577 HCAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 6 OF 30 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:278120 HCAPLUS
DOCUMENT NUMBER: 132:304290
TITLE: Therapeutic protein secretion with pharmacol. controls using fusion proteins containing conditional retention domains (CRD)
INVENTOR(S): Rivera, Victor; Clackson, Timothy; Rothman, James
PATENT ASSIGNEE(S): Ariad Gene Therapeutics, Inc., USA
SOURCE: PCT Int. Appl., 99 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000023602	A2	20000427	WO 1999-US24327	19991019

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1998-104746 19981019
US 1998-174799 19981019
US 1999-137787 19990602

AB A system for direct **pharmacol.** control of **therapeutic** protein secretion is developed by using fusion proteins which link the target **therapeutic** protein with a secretion signal sequence, one copy or multiple copies of a natural or mutated CRD, and a proteinase cleavage site (such as furin cleavage site). The CRD is any domain or its mutant which is retained in the endoplasmic reticulum (ER)or other secretory compartment in the absence of ligand and is released from the secretory machinery when its ligand is bound, such as FKBP or its F36M mutant (with Phe at the position of 36 mutated to Met) . The system is exemplified by transfecting HT88 cell lines with vector expressing a fusion protein of F36M FKBP with a human growth hormone protein (hGH) or insulin or green fluorescent protein or low-affinity nerve growth factor receptor (LNGFR), or a fusion protein of rat retinol binding domain (rRBP) with insulin. In the absence of ligands, a synthetic small-mol. **drug** like FK506, **AP21998** or **AP22542**, the secretion of the target protein is very low and most of them are retained in the ER (such as hGH or insulin or green fluorescent protein) or cellular membrane (such as LNGFR). By adding the ligand to cell culture media; a rapid and transient secretion of growth hormone and insulin can be induced several hundred fold in vitro. Using streptozotocin-**treated** mice as the disease model of **hyperglycemia**, the physiol. effects of regulated insulin secretion (a transient correction of serum glucose concns.) is also is obsd. in vivo. In addn., the invention provides methods for identifying novel CRDs using yeast two hybrid system. This approach may be used in gene **therapy** to deliver **therapeutic** proteins that require rapid and regulated expression.

L22 ANSWER 7 OF 30 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:217737 HCAPLUS
DOCUMENT NUMBER: 133:130590
TITLE: Identification of rice blast fungal elicitor-responsive genes by differential display analysis
AUTHOR(S): Kim, Cha Young; Lee, Sung-Ho; Park, Hyeong Cheol; Bae, Chang Gyu; Cheong, Yong Hwa; Choi, Young Ju; Han, Chang-Deok; Lee, Sang Yeol; Lim, Chae Oh; Cho, Moo Je

CORPORATE SOURCE: Department of Biochemistry, Gyeongsang National University, Jinju, 660-701, S. Korea
SOURCE: Mol. Plant-Microbe Interact. (2000), 13(4), 470-474
CODEN: MPMIEL; ISSN: 0894-0282
PUBLISHER: APS Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In order to study mol. interactions that occur between rice and rice blast fungus upon infection, we isolated fungal elicitor-responsive genes from rice (Oryza sativa cv. Milyang 117) suspension-cultured cells **treated** with fungal elicitor prepd. from the rice blast fungus (Magnaporthe grisea) employing a method that combined mRNA differential display and cDNA library screening. Data base searches with the isolated cDNA clones revealed that the OsERG1 and OsERG2 cDNAs share significant similarities with the mammalian Ca2+-dependent lipid binding (C2) domains. The OsCPX1 cDNA is highly homologous to peroxidases. The OsHin1 cDNA exhibits homol. to the tobacco hin1 gene, whose expression is induced by avirulent pathogens. The OsLPL1 and OsMEK1 cDNAs share homologies with lysophospholipases and serine/threonine mitogen-activated protein (MAP) kinase kinases, resp. The OsWRKY1 and OsEREBP1 cDNAs are homologous to transcription factors, such as the WRKY protein family and the **AP2** /EREBP family, resp. Transcripts of the OsERG1, OsHin1, and OsMEK1 genes were specifically elevated only in response to the avirulent race KJ301 of the rice blast fungus. Our study yielded a no. of elicitor-responsive genes that will not only provide mol. **probes**, but also contribute to our understanding of host defense mechanisms against the rice blast fungus.

REFERENCE COUNT: 22
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 8 OF 30 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:156909 HCAPLUS
DOCUMENT NUMBER: 132:260748
TITLE: Leptin is a potent anti-diabetic in mice with lipodystrophy and insulin resistance
AUTHOR(S): Berg, Jens P.
CORPORATE SOURCE: Hormone and Central Laboratory, Aker University Hospital, Oslo, 0514, Norway
SOURCE: Eur. J. Endocrinol. (2000), 142(2), 114-116
CODEN: EJOEEP; ISSN: 0804-4643
PUBLISHER: BioScientifica
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 17 refs. Recently. three transgenic mouse models of generalized lipodystrophy have been developed. In all of them the expression of specific genes was directed to white and brown fat cells through use of a vector with a regulatory sequence found in the **aP2** gene, which is adipocyte-specific. In all mouse models the physiol. features were as in patients with BSCL (Berardinelli-Seip congenital lipodystrophy). Although insulin resistance in the mice with lipodystrophy and insulin resistance could be successfully **treated** with leptin substitution, insulin sensitivity could also be improved by the thiazolidinedione, troglitazone. The effects of leptin and thiazolidinediones in mice with lipodystrophy indicate **treatment** options for **diabetes** and hyperlipidemia in patients with lipodystrophy. These lessons are important not only for the small group of patients with the congenital variant, but also for the growing no. of patients with partial lipodystrophy caused by **treatment** with HIV-1-protease inhibitors.

REFERENCE COUNT: 17

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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 9 OF 30 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:154075 HCAPLUS
DOCUMENT NUMBER: 133:69670
TITLE: Woodchuck lymphotoxin-.alpha., -.beta. and tumor necrosis factor genes: structure, characterization and biological activity
AUTHOR(S): Li, Daniel H.; Havell, Edward A.; Brown, Cynthia L.; Cullen, John M.
CORPORATE SOURCE: Department of Microbiology, Pathology and Parasitology, North Carolina State University College of Veterinary Medicine, Raleigh, NC, 27606, USA
SOURCE: Gene (2000), 242(1-2), 295-305
CODEN: GENED6; ISSN: 0378-1119
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We cloned and characterized the woodchuck tumor necrosis factor (TNF) and lymphotoxin-.alpha., -.beta. (LT-.alpha., -.beta.) cDNAs, genes and proteins to facilitate study of the functions of these cytokines during the course of woodchuck hepatitis virus (WHV) infection. Woodchuck cDNA and genomic DNA libraries were screened with woodchuck-specific DNA **probes** to isolate the cDNA and gene clones for TNF, LT-.alpha. and LT-.beta.. The cDNAs for woodchuck TNF, LT-.alpha. and LT-.beta. code for proteins of 233, 205 and 310 amino acids resp. The polypeptide encoded by each gene among woodchucks, humans and mice can differ: the human TNF, LT-.alpha. and LT-.beta. genes encode polypeptides of 233, 205 and 244 amino acids resp., whereas the mouse TNF, LT-.alpha. and LT-.beta. genes encode polypeptides of 235, 202 and 306 amino acids resp. In the woodchuck, there are four exons for TNF, four exons for LT-.alpha. and three exons for LT-.beta.. The RNA splicing patterns for TNF, LT-.alpha. and LT-.beta. genes are identical among woodchucks, humans and mice, except that the human LT-.beta. gene contains four exons. The woodchuck TNF gene promoter contains consensus sequences for binding of AP-1, **AP-2**, C/EBP.beta., CRE, Egr-1, Ets, NF-AT, NF-.kappa.B and SP-1 transcription factors. LT-.alpha. has **AP-2**, Ets, NF-.kappa.B, SP-1 and STAT binding sites, and LT-.beta. has Egr-1/SP-1, Ets and NF-.kappa.B binding sites. The bacterially expressed woodchuck TNF and LT-.alpha. proteins exhibited cytotoxic activities on both mouse L929B and woodchuck A2 cells in the presence of actinomycin D. The specific activities of TNF and LT-.alpha. were 2.62 .times. 108 units/mg and 2.22 .times. 103 units/mg resp. for L929B cells, and 1.05 .times. 109 units/mg and 3.56 .times. 104 units/mg resp. for A2 cells. However, only woodchuck TNF showed cytotoxic activity on human HepG2 cells, with a specific activity of 6.55 .times. 107 units/mg in the presence of actinomycin D. The data obtained from this study will be useful to future investigations of the TNF and LT anti-tumor and anti-viral activities, and their **therapeutic** potential in the woodchuck model for human hepatitis B virus (HBV).
REFERENCE COUNT: 39
REFERENCE(S): (1) Arch, R; Genes Dev 1998, V12, P2821 HCAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 10 OF 30 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:615905 HCAPLUS
DOCUMENT NUMBER: 132:870
TITLE: Activation of the insulin-like growth factor-binding protein-5 promoter in osteoblasts by cooperative E box, CCAAT enhancer-binding protein, and nuclear factor-1 deoxyribonucleic acid-binding sequences
AUTHOR(S): Ji, Changhua; Chen, Yun; Centrella, Michael; McCarthy, Thomas L.
CORPORATE SOURCE: Section of Plastic Surgery, Yale University School of Medicine, New Haven, CT, 06520, USA
SOURCE: Endocrinology (1999), 140(10), 4564-4572
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Insulin-like growth factor (IGF)-binding protein-5 (IGFBP-5) has IGF-dependent and -independent actions. PGE2 rapidly increases IGFBP-5 expression by osteoblasts through cAMP-dependent processes. A minimal DNA sequence required for basal and PGE2-stimulated IGFBP-5 promoter activity spans -69 to -35 bp. This region adjoins a functional TATA box and contains E box, CCAAT enhancer-binding protein (C/EBP), nuclear factor-1 (NF-1), and activator protein-2 (**AP-2**) transcription factor related binding motifs. In this study the authors compared minimal promoter sequences of -74 to +120bp, without or with mutations in each potential regulatory element, by reporter gene expression and electrophoretic mobility shift assays. Mutation of the E box-related element reduced basal promoter activity by 50% and eliminated the 2-fold stimulatory effect of PGE2. In contrast, mutations in the C/EBP- or NF-1-related elements also reduced basal promoter activity without fully eliminating the PGE2 effect. Overexpression of C/EBP.delta. stimulated basal IGFBP-5 promoter activity, and this effect was eliminated by mutating the C/EBP-binding site. However, mutation of the **AP-2**-binding site or overexpression of **AP-2** did not correlate with basal or PGE2-induced promoter activation. By electrophoretic mobility shift assay, prominent gel shift complexes occurred with osteoblast nuclear exts. and 32P-labeled **probes** spanning the E box-, C/EBP-, and NF-1-related motifs. These gel shift complexes were depleted by specific binding site mutations and were enhanced by PGE2. Increased binding by exts. from PGE2-**treated** cultures was blocked by cycloheximide **treatment**. These results identify several elements as integral binding sequences for both basal and PGE2-stimulated IGFBP-5 promoter activity. They further reveal that multiple sequences within this cluster form a basic transcription unit where nuclear factors can accumulate in a protein synthesis-dependent way and enhance IGFBP-5 expression by osteoblasts in response to PGE2.
REFERENCE COUNT: 60
REFERENCE(S): (1) Allander, S; J Biol Chem 1994, V269, P10891 HCAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 11 OF 30 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:171332 HCAPLUS
DOCUMENT NUMBER: 131:14779
TITLE: A novel method for analysis of nuclear receptor function at natural promoters: peroxisome proliferator-activated receptor .gamma. agonist actions on aP2 gene expression detected using branched DNA messenger RNA quantitation

AUTHOR(S): Burris, Thomas P.; Pelton, Patricia D.; Zhou, Lubing; Osborne, Melville C.; Cryan, Ellen; Demarest, Keith T.
CORPORATE SOURCE: Endocrine Therapeutics Department of Drug Discovery, The R.W. Johnson Pharmaceutical Research Institute, Raritan, NJ, 08869, USA
SOURCE: Mol. Endocrinol. (1999), 13(3), 410-417
CODEN: MOENEN; ISSN: 0888-8809
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Peroxisome proliferator-activated receptor-.gamma. (PPAR.gamma.), a member of the nuclear hormone receptor superfamily, plays an essential role in the mediation of the actions of **antidiabetic drugs** known as thiazolidinediones (TZDs). PPAR.gamma. activates many target genes involved in lipid anabolism including the adipocyte fatty acid binding protein (**aP2**). In this study, induction of **aP2** gene expression by PPAR.gamma. agonists was examd. in both cultured cells and **diabetic** mice using branched DNA (bDNA)-mediated mRNA quantitation. BDNA technol. allows for the direct measurement of a particular mRNA directly within cellular lysate using a 96-well plate format in a time frame comparable to a reporter gene assay. In cultured human s.c. preadipocytes, the TZDs, troglitazone and BRL-49653, both rapidly induced **aP2** mRNA as detected with the bDNA method. In these cells, the effect of BRL-49653 on **aP2** mRNA levels was detectable as early as 30 min after **treatment** (47% increase) and was maximal after 24 h of **treatment** (12-fold increase). The effects of troglitazone on **aP2** mRNA induction were similar to those of BRL-49653 except that the maximal level of induction was consistently lower (e.g. 24 h **treatment** = 4-fold increase). Dose-response relationships for both of the TZDs were also detd. using the 24-h **treatment** time point. EC50s for both BRL-49653 and troglitazone were estd. to be 80 nM and 690 nM, resp. A natural PPAR.gamma. ligand, 15-deoxy-.DELTA.12,14-PGJ2, was also active in this assay with a maximal induction of **aP2** mRNA of approx. 5-fold when tested at 1 .mu.M. Since the PPAR.gamma.:retinoid X receptor (RXR) heterodimer has been characterized as a permissive heterodimer with respect to RXR ligands, the ability of 9-cis-retinoic acid (9-cis-RA) to induce **aP2** mRNA was examd. Although 9-cis-RA had very low efficacy (2-fold induction), the maximal effect was reached at 100 nM. No synergism or additivity in **aP2** mRNA induction was detected when 9-cis-RA was included with either of the TZDs used in this study. Significant induction of **aP2** mRNA in bone marrow of db/db mice **treated** with either troglitazone or BRL-49653 was also detected, indicating that the bDNA assay may be a simple method to monitor nuclear receptor target gene induction in vivo.

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REFERENCE(S):
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 12 OF 30 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:681435 HCAPLUS
DOCUMENT NUMBER: 130:76791
TITLE: Construction and characterization of novel expression vectors for genetic adipose tissue ablation
AUTHOR(S): Ko, Duck Sung; Choi, Woong Hwan; Kim, Chul Geun
CORPORATE SOURCE: Department of Biology, College of Natural Sciences, Hanyang University, Seoul, 133-791, S. Korea
SOURCE: Korean J. Biol. Sci. (1998), 2(2), 249-258
CODEN: KJBSFZ; ISSN: 1226-5071
PUBLISHER: Korean Association of Biological Sciences
DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Obesity**, one of the most common metabolic diseases in industrial countries, is characterized by an increase in the no. or size of adipocytes. In an effort to create transgenic mouse models for the study of **obesity**, we developed a novel technique in which adipose tissue can be ablated genetically, at any specific developmental stage and/or physiol. condition, by **treatment** with ganciclovir. We made a series of adipocyte-specific expression vectors using minimal regulatory regions of brown adipocyte-specific uncoupling protein (UCP-1) gene and adipocyte-specific **aP2** gene, and then analyzed their expression characteristics in cultured cell lines. When both constructs pUCP-LacZ and paP2-LacZ were transfected transiently into differentiating 3T3-L1 (pre-white adipocytes) and HIB-1B (pre-brown adipocytes) cell lines in vitro and then monitored by X-gal staining of cells, these regulatory regions were sufficient to show proper differentiation stage-specific expression in adipocytes. To confirm that adipocytes expressing HSV-TK controlled by these minimal regulatory elements are sufficient to kill themselves with ganciclovir **treatment**, pUCP-TK and paP2-TK expression constructs were transfected stably into HIB-1B and 3T3-L1 cells, resp., and their ganciclovir sensitivities were tested during in vitro differentiation of cells. As expected, more than 80% of cells were dead by the 7th day of **treatment** with ganciclovir, while neg. control cells were not affected at all. The data suggest that the constructed vectors are suitable for obtaining novel **obese** transgenic models based on a conditional genetic tissue ablation method.

REFERENCE COUNT: 45

REFERENCE(S):
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 13 OF 30 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:649227 HCAPLUS

DOCUMENT NUMBER: 130:12984

TITLE: Abnormal regulation of the leptin gene in the pathogenesis of obesity

AUTHOR(S): Ioffe, Ella; Moon, Byoung; Connolly, Eileen; Friedman, Jeffrey M.

CORPORATE SOURCE: Howard Hughes Medical Institute, New York, NY, 10021, USA

SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1998), 95(20), 11852-11857
CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A subset of **obese** humans has relatively low plasma levels of leptin. This finding has suggested that in some cases abnormal regulation of the leptin gene in adipose tissue is etiol. in the pathogenesis of the **obese** state. The possibility that a relative decrease in leptin prodn. can lead to **obesity** was tested by mating animals carrying a weakly expressed adipocyte specific **aP2**-human leptin transgene to C57BL/6J ob/ob mice (which do not express leptin). The transgene does not contain the regulatory elements of the leptin gene and is analogous to a circumstance in which the cis elements and /or trans factors regulating leptin RNA prodn. are abnormal. The ob/ob mice carrying the transgene had a plasma leptin level of 1.78 ng/mL, which is .apprxeq. one-half that found in normal, nontransgenic mice (3.72 ng/mL). The ob/ob animals expressing the leptin transgene were markedly **obese** though not as **obese** as ob/ob mice without the transgene. The infertility as well as several of the endocrine abnormalities generally evident in ob/ob mice were normalized in the ob/ob transgenic mice. However, the ob/ob transgenic mice had an abnormal response when placed at an ambient

temp. of 4.degree., suggesting that different thresholds exist for the different biol. effects of leptin. Leptin **treatment** of the ob/ob transgenic mice resulted in marked wt. loss with efficacy similar to that seen after **treatment** of wild-type mice. In aggregate these data suggest that dysregulation of leptin gene can result in **obesity** with relatively normal levels of leptin and that this form of **obesity** is responsive to leptin **treatment**.

REFERENCE COUNT: 32
REFERENCE(S):
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 14 OF 30 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:518786 HCAPLUS
DOCUMENT NUMBER: 129:229515
TITLE: The short- and long-term effects of tumor necrosis factor-.alpha. and BRL 49653 on peroxisome proliferator-activated receptor (PPAR).gamma.2 gene expression and other adipocyte genes
AUTHOR(S): Edelstein Rosenbaum, Susan; Greenberg, Andrew S.
CORPORATE SOURCE: The USDA Human Nutrition Research Center on Aging at Tufts, Tupper Medical Research Institute New England Medical Center Boston, University and Division of Endocrinology, Boston, MA, 02111, USA
SOURCE: Mol. Endocrinol. (1998), 12(8), 1150-1160
CODEN: MOENEN; ISSN: 0888-8809
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Expression of tumor necrosis factor-.alpha. (TNF.alpha.) in adipocytes has been reported to correlate with insulin resistance assocd. with **obesity**. The thiazolidinediones such as BRL 49653 have been reported to improve insulin sensitivity in **obese** animals and humans. Although its exact mechanism of action is not known, BRL 49653 has been shown to antagonize some of the inhibitory actions of TNF.alpha.. BRL 49653 binds and activates the peroxisome proliferator-activated receptor (PPAR.gamma.2), an important nuclear transcription factor in adipocyte differentiation; however, its regulation of PPAR.gamma.2 in differentiated adipocytes is unknown. Here, the authors find that BRL 49653 blocked the ability of TNF.alpha. to down-regulate the expression and transcription of several adipocyte genes, but BRL 49653 did not prevent TNF.alpha. from down-regulating PPAR.gamma.2. Moreover, BRL 49653 alone initially decreased the expression of PPAR.gamma.2 mRNA and protein greatly. After 24 h of **treatment** in 3T3-L1 adipocytes, BRL 49653 down-regulated PPAR.gamma.2 by greater than 90% and potentiated the decrease of PPAR.gamma.2 mRNA by TNF.alpha. at this time. These unexpected results prompted the authors to repeat the expts. for a longer time to det. whether BRL 49653 would continue to down-regulate PPAR.gamma.2. With prolonged BRL 49653 **treatment**, PPAR.gamma.2 mRNA expression was not decreased as greatly, and the protein levels were decreased 20-30% below control at 72 h compared to 90% at 24 h. Although BRL 49653 continued to prevent the inhibitory effects of TNF.alpha. on perilipin and **aP2** mRNA, by 72 h, BRL 49653 was not as potent an inhibitor of TNF.alpha.'s down-regulation of perilipin protein. Since PPAR.gamma.2 protein was more abundant at this time, these results suggest that the level of PPAR.gamma.2 protein is not the sole factor that regulates the transcriptional control by BRL 49653.

L22 ANSWER 15 OF 30 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:232918 HCAPLUS
DOCUMENT NUMBER: 128:321017

TITLE: Dietary conjugated linoleic acid normalizes impaired glucose tolerance in the Zucker diabetic fatty fa/fa rat
AUTHOR(S): Houseknecht, Karen L.; Heuvel, John P. Vanden; Moya-Camarena, Silvia Y.; Portocarrero, Carla P.; Peck, Louise W.; Nickel, Kwangok P.; Belury, Martha A.
CORPORATE SOURCE: Department of Animal Sciences, Purdue University, West Lafayette, IN, 47907, USA
SOURCE: Biochem. Biophys. Res. Commun. (1998), 244(3), 678-682
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Conjugated linoleic acid (CLA) is a naturally occurring fatty acid which has anti-carcinogenic and anti-atherogenic properties. CLA activates PPAR.alpha. (peroxisome proliferator-activated receptor-.alpha.) in liver, and shares functional similarities to ligands of PPAR.gamma., the thiazolidinediones, which are potent insulin sensitizers. We provide the first evidence that CLA is able to normalize impaired glucose tolerance and improve **hyperinsulinemia** in the pre-**diabetic** ZDF rat. Addnl., dietary CLA increased steady state levels of **aP2** mRNA in adipose tissue of fatty ZDF rats compared to controls, consistent with activation of PPAR.gamma.. The insulin sensitizing effects of CLA are due, at least in part, to activation of PPAR.gamma. since increasing levels of CLA induced a dose-dependent transactivation of PPAR.gamma. in CV-1 cells cotransfected with PPAR.gamma. and PPRE X 3-luciferase reporter construct. CLA effects on glucose tolerance and glucose homeostasis indicate that dietary CLA may prove to be an important **therapy** for the prevention and **treatment** of NIDDM.

L22 ANSWER 16 OF 30 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:228122 HCAPLUS
DOCUMENT NUMBER: 129:14778
TITLE: Induction of stress response and differential expression of 70 kDa stress proteins by sodium fluoride in HeLa and rat brain tumor 9L cells
AUTHOR(S): Cheng, Ting-Jen; Chen, Tzu-Mei; Chen, Chi-Hau; Lai, Yiu-Kay
CORPORATE SOURCE: Department of Life Science, National Tsing Hua University, Hsinchu, Taiwan
SOURCE: J. Cell. Biochem. (1998), 69(2), 221-231
CODEN: JCEBD5; ISSN: 0730-2312
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We herein demonstrate that sodium fluoride (NaF) acts as a stress response inducer on HeLa and 9L rat brain tumor cells. NaF is only slightly cytotoxic, and inhibitory to Ser/Thr-phosphatases but not to Tyr-phosphatases in both cell lines. After **treatment** with 5 mM NaF for 2 h, the phosphorylation levels of vimentin and an alkali-resistant 65-kDa phosphoprotein were enhanced, a common phenomenon detected in cells under a variety of stress conditions. Under an identical **treatment** protocol, in which the cells were **treated** with 5 mM NaF for 2 h and then allowed to recover under normal growing conditions for up to 12 h, NaF differentially induced the cytoplasmic/nuclear heat-shock protein 70s (including both the inducible and the constitutively expressed members of this protein family) in HeLa cells and the endoplasmic reticulum residing heat-shock protein 70 (the glucose-regulated protein with an apparent mol. wt. of 78 kDa) in 9L cells. Electrophoretic mobility shift assays (EMSA) using **probes** contg. well-characterized regulatory elements revealed the activation of the heat-shock factor in HeLa but not in 9L cells; this is in good agreement with the stress protein induction pattern. Addnl. differential induction of binding activities toward EMSA **probes** individually contg. NF-.kappa.B, **AP-2**, and CRE-like elements were detected in NaF-**treated** cells. The possible involvement of

these binding sites as well as the corresponding factors in the stress response are discussed.

L22 ANSWER 17 OF 30 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:803316 HCAPLUS
DOCUMENT NUMBER: 128:84731
TITLE: Direct effects of leptin on brown and white adipose tissue
AUTHOR(S): Siegrist-Kaiser, Catherine A.; Pauli, Veronique; Juge-Aubry, Cristiana E.; Boss, Olivier; Pernin, Agnes; Chin, William W.; Cusin, Isabelle; Rohner-Jeanrenaud, Francoise; Burger, Albert G.; Zapf, Jurgen; Meier, Christoph A.
CORPORATE SOURCE: Unite Thyroide, Division Diabetologie, Hopital Universitaire Geneve, Universite Geneve, Geneva, CH-1211, Switz.
SOURCE: J. Clin. Invest. (1997), 100(11), 2858-2864
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Leptin is thought to exert its actions on energy homeostasis through the long form of the leptin receptor (OB-Rb), which is present in the hypothalamus and in certain peripheral organs, including adipose tissue. In this study, the authors examd. whether leptin has direct effects on the function of brown and white adipose tissue (BAT and WAT, resp.) at the metabolic and mol. levels. The chronic peripheral i.v. administration of leptin in vivo for 4 d resulted in a 1.6-fold increase in the in vivo glucose utilization index of BAT, whereas no significant change was found after intracerebroventricular administration compared with pair-fed control rats, compatible with a direct effect of leptin on BAT. The effect of leptin on WAT fat pads from lean Zucker Fa/fa rats was assessed ex vivo, where a 9- and 16-fold increase in the rate of lipolysis was obsd. after 2 h of exposure to 0.1 and 10 nM leptin, resp. In contrast, no increase in lipolysis was obsd. in the fat pads from **obese** fa/fa rats, which harbor an inactivating mutation in the OB-Rb. At the level of gene expression, leptin **treatment** for 24 h increased malic enzyme and lipoprotein lipase RNA 1.8.+-.0.17 and 1.9.+-.0.14-fold, resp., while **aP2** mRNA levels were unaltered in primary cultures of brown adipocytes from lean Fa/fa rats. Importantly, however, no significant effect of leptin was obsd. on these genes in brown adipocytes from **obese** fa/fa animals. The presence of OB-Rb receptors in adipose tissue was substantiated by the detection of its transcripts by RT-PCR, and leptin **treatment** in vivo and in vitro activated the specific STATs implicated in the signaling pathway of the OB-Rb. Taken together, our data strongly suggest that leptin has direct effects on BAT and WAT, resulting in the activation of the Jak/STAT pathway and the increased expression of certain target genes, which may partially account for the obsd. increase in glucose utilization and lipolysis in leptin-**treated** adipose tissue.

RB1.J5

L22 ANSWER 18 OF 30 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:803056 HCAPLUS
DOCUMENT NUMBER: 128:110710
TITLE: Troglitazone action is independent of adipose tissue
AUTHOR(S): Burant, Charles F.; Sreenan, Seamus; Hirano, Ken-ichi; Tai, Tzu-Ann C.; Lohmiller, Jeffrey; Lukens, John; Davidson, Nicholas O.; Ross, Susan; Graves, Reed A.
CORPORATE SOURCE: Dep. Med. Dep. Pathol., Univ. Chicago, Chicago, IL, 60637, USA
SOURCE: J. Clin. Invest. (1997), 100(11), 2900-2908
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have investigated the **antidiabetic** action of troglitazone in

aP2/DTA mice, whose white and brown fat was virtually eliminated by fat-specific expression of diphtheria toxin A chain. **AP2**/DTA mice had markedly suppressed serum leptin levels and were hyperphagic, but did not gain excess wt. **AP2**/DTA mice fed a control diet were hyperlipidemic, **hyperglycemic**, and had **hyperinsulinemia** indicative of insulin-resistant **diabetes**. **Treatment** with troglitazone alleviated the **hyperglycemia**, normalized the tolerance to i.p. injected glucose, and significantly decreased elevated insulin levels. Troglitazone also markedly decrease in serum triglycerides in a P2/DTA mice was due to a marked redn. in VLDL- and LDL-assocd. triglyceride. In skeletal muscle, triglyceride levels were decreased in **aP2**/DTA mice compared with controls, but glycogen levels were increased. Troglitazone **treatment** decreased skeletal muscle, but not hepatic triglyceride and increased hepatic and muscle glycogen content in wild-type mice. Troglitazone decreased muscle glycogen content in **aP2**/DTA mice without affecting muscle triglyceride levels. The levels of peroxisomal proliferator-activated receptor .gamma. mRNA in liver increased slightly in **aP2**/DTA mice and were not changed by troglitazone **treatment**. The results demonstrate that insulin resis tance and **diabetes** can occur in animals without significant adipose deposits. Furthermore, troglitazone can alter glucose and lipid metab. independent of its effects on adipose tissue.

L22 ANSWER 19 OF 30 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:583799 HCAPLUS
DOCUMENT NUMBER: 127:303164
TITLE: Thiazolidinediones inhibit alkaline phosphatase activity while increasing expression of uncoupling protein, deiodinase, and increasing mitochondrial mass in C3H10T1/2 cells
AUTHOR(S): Paulik, Mark A.; Lenhard, James M.
CORPORATE SOURCE: Department of Metabolic Diseases, Glaxo Wellcome Inc., Research Triangle Park, NC, 27709, USA
SOURCE: Cell Tissue Res. (1997), 290(1), 79-87
CODEN: CTSRCS; ISSN: 0302-766X
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Although there are a no. of cell lines committed to differentiate into brown adipocytes, the stem-cell origin of brown fat remains unclear. To address this problem, we explored the effects of various **pharmacol** . agents on differentiation of C3H10T1/2 cells, a pluripotent stem-cell line of mesodermal origin. Histochem. and biochem. anal. revealed that, when these cells were **treated** with retinoic acid, they expressed the osteoblastic marker alk. phosphatase. Upon addn. of thiazolidinediones and insulin, these cells accumulated lipid and expressed the adipocyte marker **aP2**, indicating differentiation into adipocytes. **Treatment** during the growth phase with thiazolidinediones resulted in maximal lipogenesis indicating a need for clonal expansion for efficient adipogenic differentiation. Further anal. revealed that addn. of thiazolidinediones to the cells increased (1) the lipolytic response of the cells to .beta.3-agonists, (2) the expression of uncoupling protein (UCP), (3) the expression of mRNA for type II iodothyronine 5'-deiodinase (5'D-II), and (4) mitochondrial staining. These results suggest the anti-**diabetic** effects of thiazolidinediones may, in part, involve increased brown adipocyte differentiation. Moreover, this is the first direct evidence indicating that brown adipocytes and osteoblasts may arise from the same stem cell.

N/A

L22 ANSWER 20 OF 30 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:142713 HCAPLUS
DOCUMENT NUMBER: 126:221413
TITLE: Functional antagonism between CCAAT/enhancer binding protein-.alpha. and peroxisome proliferator-activated receptor-.gamma. on the leptin promoter

AUTHOR(S): Hollenberg, Anthony N.; Susulic, Vedrana S.; Madura, John P.; Zhang, Bei; Moller, David E.; Tontonoz, Peter; Sarraf, Pasha; Spiegelman, Bruce M.; Lowell, Bradford B.
CORPORATE SOURCE: Division of Endocrinology, Harvard Medical School, Beth Israel Hospital, Boston, MA, 02215, USA
SOURCE: J. Biol. Chem. (1997), 272(8), 5283-5290
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The ob gene product, leptin, is a major hormonal regulator of appetite and fat cell mass. Recent work has suggested that the **antidiabetic** agents, the thiazolidinediones (TZ), which are also high affinity ligands of peroxisome proliferator-activated receptor-.gamma. (PPAR.gamma.), inhibit leptin expression in rodents. To examine the effects of this class of **drug** on the leptin gene in adipocytes we performed Northern anal. on primary rat adipocytes cultured in the presence or absence of TZ. TZ reduced leptin mRNA levels by 75%. To det. whether this effect was mediated at the transcriptional level, we isolated 6510 base pairs of 5'-flanking sequence of the leptin promoter and studied reporter constructs in primary rat adipocytes and CV-1 cells. Sequence anal. demonstrated the presence of a consensus direct repeat with a 1-base-pair gap site between -3951 and -3939 as well as a consensus CCAAT/enhancer binding protein (C/EBP) site between -55 and -47. Our functional anal. in transfected primary rat adipocytes demonstrates that, despite the presence of a canonical direct repeat with a 1-base-pair gap site, TZ alone decreases reporter gene expression of leptin promoter constructs ranging from -6510 to +9 to -65 to +9. In CV-1 cells, which contain endogenous PPAR.gamma., TZ **treatment** alone had little effect on these constructs. However, TZ **treatment** did inhibit C/EBP.alpha.-mediated trans-activation of the leptin promoter. This down-regulation of leptin reporter constructs mapped to a -65 to +9 promoter fragment which binds C/EBP.alpha. in gel-mobility shift assays but does not bind PPAR.gamma.2 alone or as a heterodimer with 9-cis-retinoic acid receptor. Conversely, the promoter (-5400 to +24 base pairs) of the **aP2** gene, another adipocyte-specific gene, was induced 7.3-fold by TZ. Co-transfection with C/EBP.alpha. minimally stimulated the **aP2** promoter from basal levels but notably blocked activation by TZ. These data indicate that PPAR.gamma. and C/EBP.alpha. can functionally antagonize each other on at least two sep. promoters and that this mechanism may explain the down-regulation of leptin expression by thiazolidinediones.

L22 ANSWER 21 OF 30 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:7888 HCAPLUS
DOCUMENT NUMBER: 126:99145
TITLE: The thiazolidinedione insulin sensitizer, BRL 49653, increases the expression of PPAR-.gamma. and aP2 in adipose tissue of high-fat-fed rats
AUTHOR(S): Pearson, S. L.; Cawthorne, M. A.; Clapham, J. C.; Dunmore, S. J.; Holmes, S. D.; Moore, G. B. T.; Smith, S. A.; Tadayyon, M.
CORPORATE SOURCE: Clore Lab., Univ. Buckingham, Buckinghamshire, MK18 1EG, UK
SOURCE: Biochem. Biophys. Res. Commun. (1996), 229(3), 752-757
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of the thiazolidinedione insulin sensitizer BRL 49653 on plasma leptin concns. and on epididymal fat OB, PPAR-.gamma. and **aP2** mRNA expression were examd. in high-fat-fed and high-carbohydrate-fed adult Wistar rats. Diets were given for 4 wk, with BRL 49653 (10 .mu.mol/kg/day) administered by oral gavage for the last 4

days. **Treatment** with BRL 49653 reduced plasma leptin concns. in high-fat-fed rats from 2.34.+-.0.19 to 1.42.+-.0.09 ng/mL. Plasma leptin was unaffected by BRL 49653 in the high-carbohydrate-fed rats. There was no difference in OB mRNA expression between high-fat-fed and high-carbohydrate-fed rats, with or without **treatment**. PPAR-.gamma. and **aP2** mRNA expression were significantly increased in the high-fat-fed rats **treated** with BRL 49653 (and resp.), but not in carbohydrate-fed rats.

L22 ANSWER 22 OF 30 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:743403 HCAPLUS
DOCUMENT NUMBER: 123:220015
TITLE: Protein-DNA interactions during phenotypic differentiation
AUTHOR(S): Dobi, A. L.; Palkovits, M.; Palkovits, C. G.; Santha, E.; Agoston, D. V.
CORPORATE SOURCE: Laboratory of Developmental Neurobiology, National Institute of Child Health and Human Development, Bethesda, MD, 20892-4480, USA
SOURCE: Mol. Neurobiol. (1995), Volume Date 1995, 10(2/3), 185-203
CODEN: MONBEW; ISSN: 0893-7648
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have been studying the mol. mechanism of neuronal differentiation through which the multipotent precursor becomes limited to the final transmitter phenotype. Here we focused on the role of the 5' proximal regulatory cassette (-190; +53 bp) of the rat enkephalin (rENK) gene in the developmental regulation of the enkephalin phenotype. Several well characterized cis-elements, including **AP2**, CREB, NF1, and NFkB, reside on this region of the rENK gene. These motifs were sufficient to confer activity-dependent expression of the gene during neuro-differentiation when it was tested using transient transfection assays of primary developing spinal cord neurons **treated** with tetrodotoxin (TTX). This region was then used as a DNA probe in mobility shift assays, with nuclear proteins derived from phenotypically and ontogenetically distinct brain regions. Only a few low abundance protein-DNA complexes were detected and only with nuclear proteins derived from developing but not from adult brain. The spatiotemporal pattern of these complexes did not show correlation with enkephalin expression which was assessed by RT-PCR. We employed synthetic **probes** corresponding to consensus as well as ENK-specific sequences of the individual motifs to identify the nature of the obsd. bands. Although both consensus NF1 and enkCRE1(NF1) formed complexes with nuclear proteins derived from the striatum and cortex at various ages, the appearance of the bands was not correlated with ENK expression. Surprisingly, no complexes were detected if other ENK-specific motifs were used as **probes**. We also tested nuclear exts. derived from forskolin-induced and control C6 glioma cells, again using the whole proximal regulatory cassette as well as individual motifs. These expts. showed the formation of elaborate protein-DNA bands. There was no direct correlation between the appearance of bands and forskolin-induced ENK expression. Unexpectedly, all ENK-specific motifs formed specific and highly abundant protein-DNA complexes when nuclear exts. from the human tumor cell line (HeLa), which does not express ENK, were used. Based on these observations, we concluded that: (1) interaction between the proximal regulatory cassette and addnl. probably far distant region of the rENK gene and their binding proteins may be necessary to confer developmentally regulated cell-specific expression of the ENK gene; and (2) inducibility of the gene by cis-elements can be governed by this region; however specificity of the induction remains elusive.

L22 ANSWER 23 OF 30 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:394030 HCAPLUS
DOCUMENT NUMBER: 122:257812
TITLE: Characterization and regulation of two testicular

inhibin/activin .beta.B-subunit messenger ribonucleic acids that are transcribed from alternate initiation sites
AUTHOR(S): Feng, Zong-Ming; Wu, AI Zhen; Chen, Ching-Ling
CORPORATE SOURCE: The Population Council, Rockefeller University, New York, NY, 10021, USA
SOURCE: Endocrinology (1995), 136(3), 947-55
CODEN: ENDOAO; ISSN: 0013-7227
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors and others have shown that the inhibin/activin .beta.B-subunit gene is expressed differently in the gonads. Two species of 4.8- and 3.7-kilobase (kb) .beta.B-subunit mRNA with equal concns. were identified in the testis, whereas 1 predominant 4.8-kb and a minor 3.7-kb mRNA were obsd. in the ovary. In this study, the authors analyzed the structures of these 2 mRNAs in rat testis and showed that both 4.8- and 3.7-kb .beta.B-subunit mRNAs were terminated at the region proximal to 2.2 kb down-stream from the translation stop codon. However, only 4.8-kb mRNA could be detected when RNA **probes** prepd. from the 5'-region 1 kb up-stream from the translation start site were used for Northern blot anal. The observations suggest that the 2 heterogeneously sized .beta.B-subunit mRNAs are transcribed from different initiation sites. Transcription of the 4.8-kb mRNA was initiated at 3 adjacent nucleotides, GGA, 1.1 kb up-stream from the translation start codon ATG, whereas multiple transcription initiation sites spreading over 150 nucleotides upstream from the ATG codon were previously identified for 3.7-kb mRNA. Neither of the 2 transcripts contained TATA and CAAT boxes in their promoters. The 5'-flanking DNAs required for transcription of the 4.8- and 3.7-kb mRNA were examd. by their ability to induce transient expression of the chloramphenicol acetyltransferase (CAT) gene in MA-10 Leydig tumor cells. A marked increase in CAT activity was detected when the 5'-flanking DNA for the 4.8- or 3.7-kb transcript was progressively shortened from its 5'-end. Maximal CAT activity was obsd. when -409 and -139 base-pair .beta.B-subunit DNA up-stream from the 4.8- and 3.7-kb transcription initiation site, resp., were fused to the CAT gene, suggesting the presence of a neg. regulatory element(s) at the up-stream regions of these promoters. Although putative **AP-2** sites were identified, **treatment** of the transfected cells with cAMP and/or phorbol 12-myristate 13-acetate did not apparently change CAT activity driven by either the 4.8- or 3.7-kb promoter. The results concluded that (1) the two inhibin/activin .beta.B-subunit mRNAs were transcribed from different initiation sites; (2) both promoters may be controlled by up-stream neg. regulatory elements; and (3) neither of these promoters is responsive to cAMP and/or phorbol esters under the conditions employed.

L22 ANSWER 24 OF 30 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:353538 HCAPLUS
DOCUMENT NUMBER: 122:232372
TITLE: Characterization of the rat light neurofilament (NF-L) gene promoter and identification of NGF and cAMP responsive regions
AUTHOR(S): Reeben, M.; Neuman, T.; Palgi, J.; Palm, K.; Paalme, V.; Saarma, M.
CORPORATE SOURCE: Inst. Biotechnol., Univ. Helsinki, Helsinki, Finland
SOURCE: J. Neurosci. Res. (1995), 40(2), 177-88
CODEN: JNREDK; ISSN: 0360-4012
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have isolated a genomic DNA clone covering the coding and 14 kb upstream region of the rat light neurofilament (NF-L) gene and sequenced 2.3 kb of its promoter. DNase I hypersensitive sites have been mapped in PC12 cells. For functional anal. of the NF-L promoter, constructs carrying 38, 97, 407, 564, 650, 1,099, 1,660, 2,003 base pairs (bp) upstream region in front of the chloramphenicol acetyltransferase (CAT) reporter gene were tested for their capability to direct CAT expression

after transient transfection into various cell lines. Similar CAT activities were recorded both in rat pheochromocytoma (PC12) and mouse neuroblastoma N115 cells and also in several nonneural cell lines (HeLa, C127, NIH 3T3). Regions responsible for the basic promoter activity were located between -407 and +75 bp from the transcription initiation site. The NGF-responsive element was located between -38 and +75 bp, and sequence -97 to -38 was found to contain a functional cAMP-responsive element. In PC12 cells in which nerve growth factor (NGF) induces neurite outgrowth and NL-L transcription, NF-L promoter-driven CAT expression was stimulated up to 12-fold within three days of NGF **treatment**, whereas epidermal growth factor (EGF) had no effect. Rat NF-L promoter contained Sp1, **AP-2** and CGCCCCCGC elements. In PC12 cells, NGF transiently induced the binding of transcription factors to the deoxyoligonucleotide **probes** contg. the binding sites of these elements. The role of these factors in NF-L gene transcriptional induction by NGF in PC12 cells is discussed.

L22 ANSWER 25 OF 30 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:475049 HCAPLUS
DOCUMENT NUMBER: 121:75049
TITLE: Identification of binding sites for transcription factors NF-.kappa.B and AP-2 in the promoter region of the human heme oxygenase 1 gene
AUTHOR(S): Avrovsky, Yan; Schwartzman, Michal L.; Levere, Richard D.; Kappas, Attallah; Abraham, Nader G.
CORPORATE SOURCE: Rockefeller University Hospital, New York, NY, 10021, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1994), 91(13), 5987-91
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Heme oxygenase (HO) is the rate-limiting enzyme in heme catabolism and its activity is induced by many agents, including its substrate heme, heavy metals, UV radiation, and other injurious oxidant conditions. The authors examd. the presence of several regulatory elements in the promoter region of the human HO-1 gene which could possibly account for its induction in response to diverse agents or influences. Heme **treatment** increased both HO activity and HO-1 mRNA in the human erythroleukemic cell line K562. Electrophoretic mobility-shift assays of nuclear protein exts. from heme-**treated** and control cells with specific oligonucleotide **probes** contg. binding sites for known transcription factors, including AP-1, **AP-2**, Sp1, NF-.kappa.B, CTF/NF1, TFIID, OKT1, and CREB, and oligonucleotides contg. serum-, metal-, and glucocorticoid-responsive elements demonstrated a specific and marked increase in the NF-.kappa.B and **AP-2** transcription factors and, to a lesser extent, an increase in AP-1. No significant increase in other transcription factors over the control, **untreated** cells was obsd. DNase I footprint assays using purified transcription factors revealed the presence of NF-.kappa.B and **AP -2** binding sites in the proximal part of the promoter region of the human HO-1 gene. Moreover, nucleotide sequence anal. of the HO-1 promoter region showed that the protected regions encompassed NF-.kappa.B and **AP-2** consensus binding sites. The presence of regulatory sequences for the binding of transcription factors such as NF-.kappa.B and **AP-2**, whose activation is assocd. with the immediate response of the cell to an injury, may be an indication of the important role which HO-1 may play in defense mechanisms against tissue injury.

L22 ANSWER 26 OF 30 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:454609 HCAPLUS
DOCUMENT NUMBER: 121:54609
TITLE: Sphingosine 1-phosphate, a novel signaling molecule, stimulates DNA binding activity of AP-1 in quiescent Swiss 3T3 fibroblasts

AUTHOR(S): Su, Yuan; Rosenthal, Dean; Smulson, Mark; Spiegel, Sarah
CORPORATE SOURCE: Med. Cent., Georgetown Univ., Washington, DC, 20007, USA
SOURCE: J. Biol. Chem. (1994), 269(23), 16512-17
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Sphingosine and sphingosine 1-phosphate, metabolites of sphingolipids, stimulate cell proliferation in quiescent Swiss 3T3 fibroblasts and induce transient increases in intracellular free calcium (Zhang, H, Desai, N. N., Olivera, A., Seki, T., Brooker, G., and Spiegel, S. (1991) J. Cell Biol. 114, 155-167). However, little is yet known of the nuclear events that follow the early responses induced by sphingolipid metabolites. Using a gel retardation assay, the authors found that specific DNA binding activity of activator protein-1 (AP-1) was markedly increased after **treatment** of quiescent Swiss 3T3 fibroblasts with sphingosine 1-phosphate and sphingosine. The DNA binding specificity of AP-1 was confirmed with competing **probes** contg. consensus sequences of AP-1, **AP-2**, AP-3, SP-1, and NF1/CTF. The c-fos gene product was detected in the AP-1 complex using anti-c-Fos antibody. The dose response for stimulation of DNA binding activity of AP-1 by sphingosine 1-phosphate correlated closely with its effect on DNA synthesis. Furthermore, an inhibitor of sphingosine kinase, DL-threo-dihydrosphingosine, which inhibits sphingosine-induced DNA synthesis and the formation of sphingosine 1-phosphate, also inhibited sphingosine-stimulated AP-1 DNA binding activity. This result further supports the authors' proposal that sphingosine 1-phosphate mediates the mitogenic effect of sphingosine. The authors' results indicate that sphingosine 1-phosphate-induced DNA synthesis and cell division may result from activation of AP-1 protein, linking signal transduction by sphingolipid metabolites to gene expression.

L22 ANSWER 27 OF 30 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:578753 HCAPLUS
DOCUMENT NUMBER: 119:178753
TITLE: Targeted expression of a toxin gene to adipose tissue: transgenic mice resistant to obesity
AUTHOR(S): Ross, Susan R.; Graves, Reed A.; Spiegelman, Bruce M.
CORPORATE SOURCE: Coll. Med., Univ. Illinois, Chicago, IL, 60612, USA
SOURCE: Genes Dev. (1993), 7(7B), 1318-24
CODEN: GEDEEP; ISSN: 0890-9369
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Obesity** is characterized by increased adipose tissue mass and is often accompanied by a no. of other disorders, such as **diabetes**, hypertension, and hyperlipidemia. To investigate the interrelationship between excessive adipose tissue mass and these assocd. disorders, an attempt was made to reduce adiposity via targeted expression of an attenuated diphtheria toxin A chain in adipose tissue, using the 5' regulatory region of the adipocyte P2 (**aP2**) gene. Transgenic mice with high levels of toxin expression developed chylous ascites and died shortly after birth. Transgenic mice expressing lower levels of the transgene had normal adiposity and survived to adulthood; however, they showed a complete resistance to chem. induced **obesity**. Nevertheless, these animals developed hyperlipidemia equal to or greater than their nontransgenic **obese** littermates. Moreover, monosodium glutamate-**treated** transgenic females were fertile, unlike their **obese** nontransgenic littermates. These data demonstrate the feasibility of genetic manipulation of adiposity and allow a functional dissection of **obesity** and its metabolic sequelae. Transgenic mice may provide useful models for the dissection of **obesity** and its clin. correlates.

L22 ANSWER 28 OF 30 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:573989 HCAPLUS

DOCUMENT NUMBER: 119:173989
TITLE: Antidiabetic agent pioglitazone enhances adipocyte differentiation of 3T3-F442A cells
AUTHOR(S): Sandouk, Tagrid; Reda, Domenic; Hofmann, Cecilia
CORPORATE SOURCE: Stritch Sch. Med., Loyola Univ., Maywood, IL, 60153, USA
SOURCE: Am. J. Physiol. (1993), 264(6, Pt. 1), C1600-C1608
CODEN: AJPHAP; ISSN: 0002-9513
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Adipocytes play an important role in normal physiol. as a major site for systemic energy homeostasis. In disorders such as **diabetes**, adipocyte function is markedly altered. In this study, the authors investigated the effect of pioglitazone, a novel **antidiabetic** agent known to lower plasma glucose in animal models of **diabetes** mellitus, on cellular differentiation and expression of adipose-specific genes. **Treatment** of confluent 3T3-F442A preadipocyte cultures for 7 days with pioglitazone (Pio; 1 .mu.M) and insulin (Ins; 0.17 .mu.M) resulted in >95% cell differentiation into lipid-accumulating adipocytes in comparison with 60-80% cell differentiation by **treatment** with either agent alone. Anal. of triglyceride accumulation showed increases of triglyceride content over time above **untreated** preadipocytes by **treatment** of the cells with Ins, Pio, and esp. with Ins + Pio. Basal glucose transport, as measured by cellular uptake of 2-deoxy-D-[14C]glucose, was likewise enhanced in a time-dependent manner by **treatment** of preadipocytes with Ins, Pio, or Ins + Pio, such that a synergistic effect resulted from the combined **treatment** with both agents. It was further detd. that RNA transcript abundance for genes encoding glucose transporters GLUT-1 and GLUT-4, as well as the adipose-specific genes encoding adipsin and **aP2**, were increased by the Ins, Pio, or Ins + Pio **treatment**. Taken together, these findings indicate that pioglitazone is a potent adipogenic agent. By promoting differentiation, this agent may move cells into a state active for glucose uptake, storage, and metab.

QP1.A5

L22 ANSWER 29 OF 30 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:53423 HCAPLUS
DOCUMENT NUMBER: 118:53423
TITLE: Structural determination and promoter analysis of the chicken mitogen-inducible prostaglandin G/H synthase gene and genetic mapping of the murine homolog
AUTHOR(S): Xie, Weilin; Merrill, Judy R.; Bradshaw, William S.; Simmons, Daniel L.
CORPORATE SOURCE: Dep. Chem., Brigham Young Univ., Provo, UT, 84602, USA
SOURCE: Arch. Biochem. Biophys. (1993), 300(1), 247-52
CODEN: ABBIA4; ISSN: 0003-9861
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The isolation and characterization of a new form (PGHS-2) of prostaglandin G/H synthase (PGHS, cyclooxygenase) from chicken embryo fibroblasts was previously reported. To further study the regulation and structure of the gene, the authors cloned the entire chicken PGHS-2 (previously termed miPGHSch) gene with its 5'-flanking region from a chicken genomic library. A genomic Southern blot showed the existence of a single PGHS-2 gene. The size of the gene was estd. at 8.9 kb through DNA sequencing and polymerase chain reaction anal. The PGHS-2 gene contains 10 exons, giving it a structure similar to that of the human PGHS-1 and murine PGHS-2 genes. The transcription start site was detd. by primer extension, and the nucleotide sequence of 1.6 kb of the 5'-flanking region immediately upstream of the transcription start site was detd. The promoter sequence contained a TATA box and a variety of enhancer elements, including a serum response element, an AP-1, an NF-.kappa.B, and several SP-1 and **AP-2** sites. Chloramphenicol acetyltransferase (CAT) assays showed that the first 158 nucleotides of the promoter efficiently drove transcription of the CAT reporter gene in serum-stimulated cells. Dexamethasone, a potent inhibitor of prostaglandin synthesis, had no

effect on CAT activity, although this **drug** is known to markedly decrease PGHS-2 mRNA in vivo. This suggests that dexamethasone may inhibit PGHS-2 mRNA expression at the post-transcriptional level. Anal. of hamster/mouse somatic cell hybrids with radiolabeled cDNA **probes** demonstrated that PGHS-1 mapped to chromosome 2 and PGHS-2 mapped to chromosome 1 of the mouse genome.

L22 ANSWER 30 OF 30 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:17822 HCAPLUS
DOCUMENT NUMBER: 114:17822
TITLE: Differentiation dependent biphasic regulation of adipsin gene expression by insulin and insulin-like growth factor-1 in 3T3-F442A adipocytes
AUTHOR(S): Lowell, Bradford B.; Flier, Jeffrey S.
CORPORATE SOURCE: Charles A. Dana Res. Inst., Beth Israel Hosp., Boston, MA, 02215, USA
SOURCE: Endocrinology (Baltimore) (1990), 127(6), 2898-906
CODEN: ENDOAO; ISSN: 0013-7227
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Because **hyperinsulinemia** is frequently assocd. with **obesity**, the effects of this hormone and insulin-like growth factor 1 (IGF-1) were detd. on on adipsin secretion and adipsin mRNA levels in 3T3-F442A adipocytes. In fully differentiated adipocytes (after 11 days postconfluence), insulin exposure progressively decreases adipsin secretion by 40, 67, and 78% after 2, 4, and 6 days of **treatment**, resp. The inhibition of adipsin secretion by insulin is the result of a corresponding decrease in adipsin mRNA and is specific since 2 other differentiation-dependent fat cell mRNAs encoding **aP2** (a fatty acid-binding protein) and glycerophosphate dehydrogenase (GPD), are unaffected. Insulin suppresses adipsin gene expression via high affinity insulin receptors, because physiol. levels of insulin produce this effect, and dose-response curves for insulin stimulation of 2-deoxyglucose uptake and glucose utilization are similar to insulin's effect on adipsin. In contrast, insulin when present during days 1-8 postconfluence (during differentiation) markedly increases adipsin secretion and adipsin mRNA levels. This stimulation is due to the ability of insulin to accelerate differentiation as evidenced by corresponding increases in **aP2** and GPD mRNAs as well. Insulin and IGF-1 are equipotent in this effect, suggesting that both insulin and IGF-1 receptors can mediate this response. Thus, during the differentiation of 3T3-F442A adipocytes, insulin stimulates adipsin gene expression by accelerating differentiation. As the cell become mature adipocytes, they acquire some differentiation-dependent factor, which coupled insulin receptor stimulation to inhibition of adipsin gene expression. This model should aid the search for the mol. links between insulin receptor stimulation and altered gene expression.

=> d stat que l26 nos

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L6              STR
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                OR ?HYPERGLYCEROL?)
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L23          443 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L16(L)INHIBIT?
L25           18 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L23 AND L19
L26            7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L25 NOT (L8 OR L11 OR L18 OR
                 L22)


=> d ibib abs hitrn l26 1-7


L26  ANSWER 1 OF 7  HCAPLUS  COPYRIGHT 2001 ACS
ACCESSION NUMBER:         1998:784882  HCAPLUS
DOCUMENT NUMBER:          130:148506
TITLE:                    A novel insulin sensitizer acts as a coligand for
                          peroxisome proliferator-activated receptor-.alpha.
                          (PPAR-.alpha.) and PPAR-.gamma.: effect of
                          PPAR-.alpha. activation on abnormal lipid metabolism
                          in liver of Zucker fatty rats
AUTHOR(S):                Murakami, Koji; Tobe, Kazuyuki; Ide, Tomohiro;
                          Mochizuki, Toshiro; Ohashi, Mitsuo; Akanuma, Yasuo;
                          Yazaki, Yoshio; Kadowaki, Takashi
CORPORATE SOURCE:         Third Department of Internal Medicine, Faculty of
                          Medicine, University of Tokyo, Tokyo, 113, Japan
SOURCE:                   Diabetes (1998), 47(12), 1841-1847
                          CODEN: DIAEAZ; ISSN: 0012-1797
PUBLISHER:                American Diabetes Association
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   We investigated the biol. activity of a novel thiazolidinedione (TZD)
     deriv., KRP-297, and the mol. basis of this activity.  When administered
     to obese Zucker fatty rats (obese rats) at 10 mg/kg
     for 2 wk, KRP-297, unlike BRL-49653, restored reduced lipid oxidn., i.e.,
     CO2 and ketone body prodn. from [14C]palmitic acid, in the liver by 39% (P
     < 0.05) and 57% (P < 0.01), resp.  KRP-297 was also significantly more
     effective than BRL-49653 in the inhibition of enhanced
     lipogenesis and triglyceride accumulation in the liver.  To understand the
     mol. basis of the biol. effects of KRP-297, we examd. the effect on
     peroxisome proliferator-activated receptor (PPAR) isoforms, which may play
     key roles in lipid metab.  Unlike classical TZD derivs., KRP-297 activated
     both PPAR-.alpha. and PPAR-.gamma., with median effective concns. of 1.0
     and 0.8 .mu.mol/L, resp.  Moreover, radiolabeled [3H]KRP-297 bound
     directly to PPAR-.alpha. and PPAR-.gamma. with dissocn. consts. of 228 and
     326 nmol/L, resp.  Concomitantly, KRP-297, but not BRL-49653, increased
     the mRNA and the activity (1.5-fold [P < 0.01] and 1.8-fold [P < 0.05],
     resp.) of acyl-CoA oxidase, which has been reported to be regulated by
     PPAR-.alpha., in the liver.  By contrast, KRP-297 (P < 0.05) was less
     potent than BRL-49653 (P < 0.01) in inducing the PPAR-.gamma.-regulated
     aP2 gene mRNA expression in the adipose tissues.  These results
     suggest that PPAR-.alpha. agonism has a protective effect against abnormal
     lipid metab. in liver of obese rats.
REFERENCE COUNT:          35
REFERENCE(S):             (1) Aoyama, T; J Biol Chem 1998, V273, P5678 HCAPLUS
                          (2) Auboeuf, D; Diabetes 1997, V46, P1319 HCAPLUS
                          (3) Berry, M; J Cell Biol 1969, V43, P506 HCAPLUS
                          (5) Braissant, O; Endocrinology 1996, V137, P354
                              HCAPLUS
                          (7) Eacho, P; Biochem Biophys Res Commun 1988, V157,
                              P1148 HCAPLUS
                          ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26  ANSWER 2 OF 7  HCAPLUS  COPYRIGHT 2001 ACS
ACCESSION NUMBER:         1997:485978  HCAPLUS
```

TITLE: Identification of the polyphosphoinositide binding site of assembly proteins IP-180 and AP-2 with photoaffinity analogs.
AUTHOR(S): Mehrotra, Bharat; Profit, Adam A.; Prestwich, Glenn D.
CORPORATE SOURCE: Department Medicinal Chemistry, University Utah, Salt Lake City, UT, 84112, USA
SOURCE: Book of Abstracts, 214th ACS National Meeting, Las Vegas, NV, September 7-11 (1997), CARB-022. American Chemical Society: Washington, D. C.
CODEN: 64RNAO
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English

AB Inositol polyphosphates (IPn) and polyphosphoinositides (PIPn) play an important role in exo- and endocytosis at nerve terminals. These ligands bind with high affinity to synaptotagmin C2B domain and various assembly proteins (**AP-2** and AP-180, a.k.a., AP-3). AP-180, expressed in the presynaptic terminals of neuronal cells, is crit. for synaptic vesicle biogenesis and recycling. It has been recently shown that PI(3,4,5)P3 is a high affinity ligand and a potent **inhibitor** of clathrin assembly. We are studying the specificity of various IPn and PIPn derivs. towards AP-180 using photoaffinity labeling. These **photoprobes** have a 4-benzoyldihydrocinnamidyl (BZDC) photophore that covalently attaches to the protein upon activation. We are also using IPn and PIPn photoaffinity analogs to det. the binding sites for the **AP-2** .alpha.-subunit and N-terminus 33 kD fragment of AP-180.

L26 ANSWER 3 OF 7 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:50090 HCAPLUS
DOCUMENT NUMBER: 126:142399
TITLE: Absence of MEF2 binding to the A/T-rich element in the muscle creatine kinase (MCK) enhancer correlates with lack of early expression of the MCK gene in embryonic mammalian muscle
AUTHOR(S): Ferrari, Stefano; Molinari, Susanna; Melchionna, Roberta; Cusella-De Angelis, Maria Gabriella; Battini, Renata; De Angelis, Luciana; Kelly, Robert; Cossu, Giulio
CORPORATE SOURCE: Dip. Scienze Biomediche, Univ. Modena, Modena, 41100, Italy
SOURCE: Cell Growth Differ. (1997), 8(1), 23-34
CODEN: CGDIE7; ISSN: 1044-9523
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB During skeletal muscle development, different types of muscle fibers are generated, which express different combinations of muscle-specific gene products. For example, the muscle creatine kinase gene (MCK) is highly expressed in fetal but not embryonic myotubes. We performed transient transfections of CAT reporter constructs, driven by the MCK promoter with variable lengths of 5'-flanking sequence, into primary cultures of embryonic and fetal muscle cells. Reporter activity was obsd. in fetal but not embryonic muscle cells. We assayed the ability of nuclear exts. prepd. from embryonic and fetal muscle and C2C12 myotubes to bind specific regulatory elements in the MCK enhancer. The profile of DNA/protein complexes resulting from electrophoretic mobility shift assays was qual. the same with all exts. used when the oligonucleotide **probes** represented the MCK E-box, MHox site, CArG-box, and **AP2** site. In contrast, no binding activity to the MEF2 site was obsd. with embryonic nuclear ext. Interestingly, MEF2 mRNAs and proteins were detected in both fetal and embryonic muscle, with the exception of the MEF2D1b isoform, which is restricted to fetal muscle. Furthermore, we found that protein phosphatase **inhibitors** included in the prepn. of embryonic nuclear exts. or added to the medium of transfected embryonic myotubes can restore MEF2 DNA binding activity, as well as reporter activity driven by the MCK promoter and partial transcriptional activation of the endogenous

MCK gene. We propose that phosphorylation of MEF2 regulates its activity and represents an important aspect of the mechanism controlling stage-specific transcription during skeletal myogenesis.

L26 ANSWER 4 OF 7 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:522355 HCAPLUS
DOCUMENT NUMBER: 125:213720
TITLE: Structural organization and chromosomal assignment of the human 14-3-3 .eta. chain gene (YWHAH)
AUTHOR(S): Muratake, Tatsuyuki; Hayashi, Shigenobu; Ichikawa, Tomio; Kumanishi, Toshiro; Ichimura, Yuka; Kuwano, Ryozo; Isobe, Toshiaki; Wang, Yimin; Minoshima, Shinsei; et al.
CORPORATE SOURCE: National Saigata Hospital, Nakakubiki, 949-31, Japan
SOURCE: Genomics (1996), 36(1), 63-69
CODEN: GNMCEP; ISSN: 0888-7543
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 14-3-3 Protein, a brain-specific protein, is thought to be a multifunctional protein involved in the activation of tyrosine and tryptophan hydroxylases, the **inhibition** or activation of protein kinase C, and the activation of signal transduction. The human 14-3-3 .eta. chain gene was isolated and its structure was detd. It is composed of two exons sepd. by one long intron (approx. 8 kb) and spans about 10 kb. A transcription initiation site was identified by a combination of S1 nuclease mapping, primer extension anal., and RACE methods. In the 5'-flanking region, the authors found four GC box sequences, four anti-GC box sequences, a TATA box-like sequence, CAAT box-like sequences, a C/EBP element, two **AP-2** sequences, an AP-3 sequence, an Oct-6-like sequence, six E boxes, and a CRE sequence. FISH with DNA **probes** of the human 14-3-3 .eta. chain gene mapped the 14-3-3 .eta. chain gene to chromosome 22q12.1-q13.1.

L26 ANSWER 5 OF 7 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:318242 HCAPLUS
DOCUMENT NUMBER: 120:318242
TITLE: Pyridoxal 5'-phosphate probes at Lys-480 can sense the binding of ATP and the formation of phosphoenzymes in Na+,K+-ATPase
AUTHOR(S): Kaya, Shunji; Tsuda, Takeo; Hagiwara, Kaoru; Fukui, Toshio; Taniguchi, Kazuya
CORPORATE SOURCE: Fac. Sci., Hokkaido Univ., Sapporo, 060, Japan
SOURCE: J. Biol. Chem. (1994), 269(10), 7419-22
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Lys-480 in .alpha. subunits of (Na+,K+)-ATPase from pig kidneys was specifically modified with pyridoxal 5'-phosphate (PLP) or pyridoxal 5'-diphospho-5'-adenosine (**AP2PL**) **probes** in the presence of NaCl. The site was shown to be the same as the previously reported ATP-protectable binding of these **probes**. The modifications strongly reduced both (Na+,K+)-ATPase activity and the amt. of Na+-dependent phosphoenzyme from [32P]ATP but not from [32P]acetyl-phosphate (AcP). The addn. of AcP to the enzyme induced a slight decrease in the fluorescence of the PLP probe in the presence of 2M NaCl and 4 mM MgCl2, but a single exponential increase in the presence of 16 mM NaCl and 4 mM MgCl2. The addn. of ATP induced single exponential fluorescence increases at both Na+ concns. The data showed that these **probes** could sense mol. events related to the formation of phosphoenzymes induced by AcP and presumably to the formation of the Mg-Na-ATP-enzyme complex. The data also suggested that PLP or **AP2PL probes** at Lys-480 in the presence of Na+ and Mg2+ did not affect the transphosphorylation from AcP to Asp-369 to form phosphoenzymes, but that they **inhibited** the transphosphorylation from the .gamma.-phosphoryl group of ATP and also ATP binding in the absence of Mg2+.

L26 ANSWER 6 OF 7 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:181266 HCAPLUS
DOCUMENT NUMBER: 114:181266
TITLE: Adenine nucleotide-binding sites on mitochondrial F1-ATPase. Evidence for an adenylate kinase-like orientation of catalytic and noncatalytic sites
AUTHOR(S): Vogel, Pia D.; Cross, Richard L.
CORPORATE SOURCE: Health Sci. Cent., State Univ. New York, Syracuse, NY, 13210, USA
SOURCE: J. Biol. Chem. (1991), 266(10), 6101-5
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Nucleotide-depleted mitochondrial F1-ATPase (F1[0,0]) is **inhibited** by the diadenosine oligophosphates, AP4A, AP5A, and AP6A (where APxA stands for 5',5'-diadenosine oligophosphates having a chain of x phosphoryl groups linking the 2 adenosine moieties). When F1[0,0] is preincubated with these compds. and then assayed for ATP hydrolysis activity under conditions that normally allow turnover at all 3 catalytic sites, the maximal level of **inhibition** obsd. is 80%. However, when assayed at lower ATP concns. under conditions that allow simultaneous turnover at only 2 of the 3 sites, no **inhibition** is obsd. A decrease in the no. of phosphoryl groups that links the adenosine moieties to <4 (AP3A, **AP2A**) converts the compd. to an activator of ATP hydrolysis, similar in effect to that obtained when 1 mol of ADP or 2-azido-ADP binds at a catalytic site on F1[0,0]. **Inhibition** by the compds. requires the presence of at least 1 vacant noncatalytic site. Evidence is provided that the **probes** also interact with a catalytic site. The stoichiometry for maximal **inhibition** by AP4A is 0.94 mol/mol of F1. The data presented support a model for the structure of nucleotide-binding sites on F1 that places catalytic and noncatalytic sites in close proximity in an orientation analogous to the ATP and AMP binding sites on adenylate kinase. **Inhibition** of the enzyme by the dinucleotide compds. can be explained by the cross-bridging of 1 of the catalytic sites to a noncatalytic site in analogy to the **inhibition** of adenylate kinase by AP5A. The residual capacity for bi-site catalysis indicates that the 2nd and 3rd catalytic sites remain catalytically active.

L26 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1987:435590 HCAPLUS
DOCUMENT NUMBER: 107:35590
TITLE: Loss of unisite and multisite catalyses by Escherichia coli F1 through modification with adenosine tri- or tetraphosphopyridoxal
AUTHOR(S): Noumi, Takato; Tagaya, Mitsuo; Miki-Takeda, Keiko; Maeda, Masatomo; Fukui, Toshio; Futai, Masamitsu
CORPORATE SOURCE: Inst. Sci. Ind. Res., Osaka Univ., Osaka, 567, Japan
SOURCE: J. Biol. Chem. (1987), 262(16), 7686-92
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Pyridoxal phosphate (PLP) and adenosine diphospho (**AP2**-PL)-, triphospho (AP3-PL)-, and tetraphospho (AP4-PL)-pyridoxals were tested as potential affinity **probes** for F1 ATPase of E. coli. Both AP3-PL and AP4-PL bound and **inhibited** F1 ATPase, whereas PLP and **AP2**-PL were weak **inhibitors**. The concns. of AP3-PL and AP4-PL for half-maximal inactivations of the multisite (steady state) ATPase activity were both 18 .mu.M. The binding of these reagents to a reactive lysyl residue(s) was confirmed from the difference absorption spectra, and the stoichiometry of binding of [3H]AP3-PL to F1 at the satg. level was .apprx.1 mol/mol F1. The analog bound to both the .alpha. subunit (.apprx.2/3 of the radioactivity) and the .beta. subunit (.apprx.1/3 of the radioactivity). No inactivation of multisite ATPase activity or binding of AP3-PL was obsd. in the presence of ATP. F1

modified with .apprx.1 mol of AP3-PL had essentially no uni- and multisite hydrolysis of ATP. The rate of binding of ATP decreased to 10-2 of that of unmodified F1, and the rate of release of ATP was .apprx.2-fold faster. The equil. F1.cntdot.ATP.dblharw.F1.cntdot.ADP.cntdot.Pi (where Pi is inorg. phosphate) was shifted toward F1.cntdot.ATP, and no promotion of ATP hydrolysis at unisite was obsd. with excess ATP. These results suggest that the AP3-PL or AP4-PL bound to an active site, and catalysis by the 2 remaining sites was completely abolished.

=> d stat que l40 nos

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L11           1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L10 NOT L8
L13       13312 SEA FILE=REGISTRY ABB=ON  PLU=ON  OXAZOLE?/CN
L14         173 SEA FILE=REGISTRY ABB=ON  PLU=ON  AP2?
L15       31521 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L13 OR ?OXAZOLE?
L16        2486 SEA FILE=HCAPLUS ABB=ON  PLU=ON  AP2? OR AP(W)2 OR L14
L17           3 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L16 AND L15
L18           1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L17 NOT (L8 OR L11)
L19          98 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L16(L)(?DIABET? OR ?OBES? OR
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L25          18 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L23 AND L19
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                 OR ?DRUG? OR ?THERAP?)
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                 L22 OR L26)
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=> d ibib abs hitrn l40 1-20

L40 ANSWER 1 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:809620 HCAPLUS
DOCUMENT NUMBER: 134:110217
TITLE: Induction of adipocyte-specific gene expression is correlated with mammary tumor regression by the retinoid X receptor-ligand LGD1069 (Targretin)
AUTHOR(S): Agarwal, Veena R.; Bischoff, Eric D.; Hermann, Thomas; Lamph, William W.
CORPORATE SOURCE: Department of Nuclear Receptor Discovery, Ligand Pharmaceuticals Inc., San Diego, CA, 92121, USA
SOURCE: Cancer Res. (2000), 60(21), 6033-6038
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Targretin (LGD1069; a high-affinity ligand for the retinoid X receptors) is an efficacious **chemotherapeutic** and chemopreventive agent in the N-nitroso-N-methylurea-induced rat mammary carcinoma model. To evaluate the mol. action of LGD1069 in mammary carcinoma we have examd.

gene expression patterns in controls and nonresponding tumors compared with tumors undergoing regression (responding) by LGD1069. When compared with controls or nonresponding tumors, the expression of adipocyte-related genes such as adipocyte P2 (**aP2**), adipsin, peroxisome proliferator-activated receptor .gamma. (PPAR.gamma.), and lipoprotein lipase was elevated in LGD1069-responding tumors. Further anal. showed that gene expression changes occurred rapidly, in as little as 6 h, after the first dose of LGD1069. Immunohistochem. anal. showed that **aP2 protein** was also highly expressed in responding tumors when compared with control or nonresponding tumors. More importantly, **aP2 protein** was localized in the tumor cells in addn. to the adipocytes present in the tumors. Similar changes in gene expression and **inhibition** in growth were seen in tumor cells (cloned from N-nitroso-N-methylurea-induced carcinoma) exposed to LGD1069 in vitro. These data suggest that tumor regression by LGD1069 involves differentiation induction along the adipocyte lineage.

REFERENCE COUNT: 39
REFERENCE(S): (1) Amy, C; Proc Natl Acad Sci USA 1989, V86, P3114 HCAPLUS
(3) Anzano, M; Cancer Res 1994, V54, P4614 HCAPLUS
(4) Bischoff, E; Cancer Res 1998, V58, P479 HCAPLUS
(5) Bischoff, E; J Natl Can Inst 1999, V91, P2118 HCAPLUS
(6) Boehm, M; J Med Chem 1994, V37, P2930 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L40 ANSWER 2 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:573930 HCAPLUS
DOCUMENT NUMBER: 133:159935
TITLE: Inhibiting formation of atherosclerotic lesions by reducing adipocyte fatty acid binding protein (AFABP)
INVENTOR(S): Haber, Edgar; Lee, Mu-en; Perrella, Mark A.; Hotamisligil, Gokhan S.
PATENT ASSIGNEE(S): President and Fellows of Harvard College, USA; Haber, Carol
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000047734	A1	20000817	WO 2000-US3560	20000211

W: AU, CA, JP, US
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRIORITY APPLN. INFO.: US 1999-119880 19990212

AB The invention features a method of **inhibiting** formation of atherosclerotic lesions by administering to a mammal, e.g., a human patient who has been identified as suffering from or at risk of developing atherosclerosis, a compd. that reduces expression or activity of adipocyte fatty acid binding **protein** (AFABP or **aP2**).
Inhibiting AFABP expression or activity reduced the development of atherosclerotic lesions despite a high level of serum cholesterol. Mice with a null mutation in the genes for apoE or both apoE and AFABP were used for the study.

IT **140602-12-6**
RL: PRP (Properties)
(unclaimed nucleotide sequence; **inhibiting** formation of atherosclerotic lesions by reducing adipocyte fatty acid binding **protein** (AFABP))

REFERENCE COUNT: 9
REFERENCE(S): (1) Dana Farber Cancer Inst Inc; WO 9206104 A 1992 HCAPLUS

(2) Horvai, A; PROC NATL ACAD SCI U S A 1995, V92(12), P5391 HCAPLUS
(3) Hotamisligil, G; SCIENCE 1996, V274(5291), P1377 HCAPLUS
(4) Incyte Pharma Inc; WO 9845440 A 1998 HCAPLUS
(5) Lyle, R; BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS 1996, V228(3), P709 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L40 ANSWER 3 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:542169 HCAPLUS
DOCUMENT NUMBER: 133:160251
TITLE: Multipotential mesenchymal stem cell adipocyte differentiation by prolactin induction of CCAAT enhancer-binding protein-.beta. and peroxisome proliferator-activated receptor .gamma. expression and screening of adipocyte differentiation regulators
INVENTOR(S): Wakao, Rika; Wakao, Hiroshi
PATENT ASSIGNEE(S): Helix Research Institute, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 18 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2000217576	A2	20000808	JP 1999-24625	19990202
WO 2000046348	A1	20000810	WO 2000-JP567	20000202

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: JP 1999-24625 19990202

AB A method for inducing adipocyte differentiation of multipotential mesenchymal stem cells by culturing multipotential mesenchymal stem cells in the presence of prolactin is disclosed. The method also includes addn. of peroxisome proliferator-activated receptor .gamma. (PPAR.gamma.) activator and expression of exogenous prolactin receptor in multipotential mesenchymal stem cells, NIH-3T3 cells in particular. A method of screening for adipocyte differentiation **inhibitors** or activators is also claimed. These compds. include **inhibitors** or activators of prolactin, prolactin receptor, C/EBP.beta. or PPAR.gamma. expression inducer, and prolactin signal transduction **inhibitors** or activators. Extracellular stimuli trigger adipocyte differentiation by inducing the complex cascades of transcription. Transcription factors CCAAT enhancer-binding **proteins** (C/EBPs) and peroxisome proliferator-activated receptor .gamma. (PPAR.gamma.) play crucial roles in this process. Although ectopic expression of these factors in NIH-3T3 cells, a multipotential mesenchymal stem cell line, results in adipogenic conversion, little is known as to hormonal factors that regulate adipogenesis in these cells. The authors demonstrate that PRL, a lactogenic hormone, enhances C/EBP.beta. and PPAR.gamma. mRNA expression and augments adipogenic conversion of NIH-3T3 cells. Moreover, the authors show that ectopic expression of the PRL receptor in NIH-3T3 cells results in efficient adipocyte conversion when stimulated with PRL and a PPAR.gamma. ligand, as evidenced by expression of the adipocyte differentiation-specific genes as well as the presence of fat-laden cells. The authors further demonstrate that signal transducer and activator of transcription 5 (Stat5), a PRL signal transducer, activates **aP2**

promoter in a PRL-dependent manner. These results suggest that PRL acts as an adipogenesis-enhancing hormone in NIH-3T3 cells.

L40 ANSWER 4 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:444225 HCAPLUS
DOCUMENT NUMBER: 133:333056
TITLE: Expression of transcription factor AP-2.alpha. predicts survival in epithelial ovarian cancer
AUTHOR(S): Anttila, M. A.; Kellokoski, J. K.; Moisio, K. I.; Mitchell, P. J.; Saarikoski, S.; Syrjanen, K.; Kosma, V-M.
CORPORATE SOURCE: Departments of Obstetrics and Gynecology, Pathology and Forensic Medicine, University of Kuopio and Kuopio University Hospital, Kuopio, FIN-70211, Finland
SOURCE: Br. J. Cancer (2000), 82(12), 1974-1983
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Harcourt Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The 52-kDa activator **protein** (**AP**)-**2** is a DNA-binding transcription factor which has been reported to have growth **inhibitory** effects in cancer cell lines and in human tumors. In this study the expression of **AP-2**.alpha. was analyzed in 303 epithelial ovarian carcinomas by immunohistochem. (IHC) with a polyclonal **AP-2**.alpha. antibody and its mRNA status was detd. by in situ hybridization (ISH) and reverse transcriptase-polymerase chain reaction (RT-PCR). The immunohistochem. expression of **AP-2**.alpha. was correlated with clinicopathol. variables, p21/WAF1 **protein** expression and survival. In normal ovaries, epithelial cells expressed **AP-2**.alpha. **protein** only in the cytoplasm. In carcinomas nuclear **AP -2**.alpha. expression was obsd. in 28% of the cases although cytoplasmic expression was more common (51%). The expression of **AP-2**.alpha. varied according to the histol. subtype and differentiation. **AP-2**.alpha. and p21/WAF1 expressions did not correlate with each other. Both in univariate (P = 0.002) and multivariate analyses (relative risks (RR) 1.6, 95% confidence interval (CI) 1.13-2.18, P = 0.007) the high cytoplasmic **AP-2** .alpha. expression favored the overall survival. In contrast, the nuclear **AP-2**.alpha. expression combined with low cytoplasmic expression increased the risk of dying of ovarian cancer (RR = 2.10, 95% CI 1.13-3.83, P = 0.018). The shift in the expression pattern of **AP-2**.alpha. (nuclear vs cytoplasmic) in carcinomas points out to the possibility that this transcription factor may be used by oncogenes in certain histol. subtypes. Based on the mRNA analyses, the incomplete expression and translation of **AP-2**.alpha. in ovarian cancer may be due to post-transcriptional regulation.
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L40 ANSWER 5 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:738016 HCAPLUS
DOCUMENT NUMBER: 132:44542
TITLE: Inhibition of adipocyte differentiation by HIV protease inhibitors
AUTHOR(S): Zhang, Bei; Macnaul, Karen; Szalkowski, Deborah; Li, Zhihua; Berger, Joel; Moller, David E.
CORPORATE SOURCE: Department of Metabolic Disorders, Merck Research Laboratories, Rahway, NJ, 07065, USA

SOURCE: J. Clin. Endocrinol. Metab. (1999), 84(11), 4274-4277
CODEN: JCEMAZ; ISSN: 0021-972X
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Patients with AIDS who are receiving **therapy** with HIV protease **inhibitors** have been widely reported to be afflicted with a syndrome characterized by lipodystrophy (fat redistribution favoring the accumulation of abdominal and cervical adipose tissue), hyperlipidemia, and insulin resistance. HIV protease **inhibitors** have been suggested to have a direct role in modulating adipocyte differentiation. To address this hypothesis, several HIV protease **inhibitors** were studied for their ability to either augment or **inhibit** the differentiation of murine 3T3-L1 preadipocytes. Dose-responsive **inhibition** of adipogenesis by several protease **inhibitors** was noted as measured by reduced triglyceride accumulation and attenuated induction of three differentiation marker genes - **aP2**, lipoprotein lipase, and Adipo Q. Potential mechanisms for altered adipocyte function, including direct binding to PPAR.gamma. or **inhibition** of PPAR.gamma.-mediated gene transcription were effectively excluded.
REFERENCE COUNT: 12
REFERENCE(S): (1) Berger, J; J Biol Chem 1999, V274, P6718 HCAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L40 ANSWER 6 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:141422 HCAPLUS
DOCUMENT NUMBER: 131:28828
TITLE: Differential sensitivity of transcription factors to mustard-damaged DNA
AUTHOR(S): Chen, Xin-Ming; Gray, Peter J.; Cullinane, Carleen; Phillips, Don R.
CORPORATE SOURCE: Department of Biochemistry, La Trobe University, Bundoora, 3083, Australia
SOURCE: Chem.-Biol. Interact. (1999), 118(1), 51-67
CODEN: CBINA8; ISSN: 0009-2797
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Nitrogen mustard (bis(2-chloroethyl)methylamine, HN2) **inhibited** the binding of upstream factors Sp1 and **AP2** to their consensus sequences. At concns. where 50% of the consensus sequence DNA contained at least one lesion, HN2 **inhibited** formation of the Sp1 complex by 37% (40 .mu.M HN2) and the **AP2** complex by 40% (50 .mu.M HN2). The binding of the TATA binding **protein** (TBP) to the TATA element was also **inhibited** by HN2, whereas sulfur mustard and the monofunctional sulfur mustard 2-chloroethyl Et sulfide (CEES) resulted in a disproportional extent of **inhibition** with respect to the level of alkylation. The level of alkylation of the TBP oligonucleotide varied significantly at 100 .mu.M **drug**, with 80, 42 and 15% of HN2, sulfur mustard and CEES, resp. However, this level of alkylation **inhibited** formation of the TBP-DNA complex by 70, 70 and 45%, resp. This differential sensitivity of transcription factors to mustard-induced DNA damage therefore appears to reside dominantly in the stereochem. differences between the specific mustard lesions.
REFERENCE COUNT: 46
REFERENCE(S): (1) Bellorini, M; Nucleic Acids Res 1995, V23, P1657 HCAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L40 ANSWER 7 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:19294 HCAPLUS
DOCUMENT NUMBER: 130:180556
TITLE: A potential role for the nuclear factor of activated T cells family of transcriptional regulatory proteins in adipogenesis
AUTHOR(S): Ho, I-Cheng; Kim, John H.-J.; Rooney, John W.; Spiegelman, Bruce M.; Glimcher, Laurie H.
CORPORATE SOURCE: Department of Immunology and Infectious Diseases, Harvard School of Public Health, Boston, MA, 02115, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1998), 95(26), 15537-15541
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB NFAT (nuclear factor of activated T cells) is a family of transcription factors implicated in the control of cytokine and early immune response gene expression. Recent studies have pointed to a role for NFAT **proteins** in gene regulation outside of the immune system. Herein we demonstrate that NFAT **proteins** are present in 3T3-L1 adipocytes and, upon fat cell differentiation, bind to and transactivate the promoter of the adipocyte-specific gene **aP2**. Further, fat cell differentiation is **inhibited** by cyclosporin A, a **drug** shown to prevent NFAT nuclear localization and hence function. Thus, these data suggest a role for NFAT transcription factors in the regulation of the **aP2** gene and in the process of adipocyte differentiation.
REFERENCE COUNT: 53
REFERENCE(S): (1) Beals, C; Genes Dev 1997, V11, P824 HCAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L40 ANSWER 8 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:801181 HCAPLUS
DOCUMENT NUMBER: 130:151497
TITLE: Bcl-2-mediated resistance to apoptosis is associated with glutathione-induced **inhibition** of **AP24** activation of nuclear DNA fragmentation
AUTHOR(S): Wright, Susan C.; Wang, Hong; Wei, Qi Sheng; Kinder, David H.; Larrick, James W.
CORPORATE SOURCE: Palo Alto Institute of Molecular Medicine, Mountain View, CA, 94043, USA
SOURCE: Cancer Res. (1998), 58(23), 5570-5576
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: AACR Subscription Office
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Studies on the mechanism of apoptosis in this lab. support a model in which signal transduction involving caspase 3 leads to activation of a serine protease called Mr 24,000 apoptotic protease (AP24), which then induces internucleosomal DNA fragmentation in the nucleus. This study examd. the effect of Bcl-2 overexpression on activation of AP24 and the induction of DNA fragmentation by AP24 in isolated nuclei. It was demonstrated that overexpression of Bcl-2 in either HL-60 or PW leukemia cell lines suppressed activation of AP24 induced by either tumor necrosis factor or UV light and protected cells from apoptosis. Furthermore, nuclei isolated from Bcl-2-overexpressing cells were relatively resistant to internucleosomal DNA fragmentation induced by AP24 isolated from

apoptotic cells. Bcl-2-overexpressing cells that were nutritionally depleted of glutathione (GSH) became sensitive to tumor necrosis factor- or UV light-induced activation of AP24 and underwent apoptotic cell death. Moreover, nuclei isolated from Bcl-2-overexpressing cells that were depleted of GSH became sensitive to AP24-induced DNA fragmentation. The addn. of exogenous GSH blocked the proteolytic activity of AP24, as well as its ability to induce DNA fragmentation in normal isolated nuclei. These results indicate that Bcl-2 can attenuate at least two events in the AP24 apoptotic pathway: activation of AP24 and induction of DNA fragmentation by activated AP24. Furthermore, agents that deplete intracellular levels of GSH may have **therapeutic** use in the sensitization of Bcl-2-overexpressing cancer cells to apoptotic cell death.

REFERENCE COUNT: 46
REFERENCE(S): (1) Backway, K; Cancer Res 1997, V57, P2446 HCAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L40 ANSWER 9 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:342417 HCAPLUS
DOCUMENT NUMBER: 129:93317
TITLE: Transcriptional induction of cyclooxygenase-2 gene by okadaic acid inhibition of phosphatase activity in human chondrocytes: co-stimulation of AP-1 and CRE nuclear binding proteins
AUTHOR(S): Miller, Caroline; Zhang, Mengkun; He, Yulan; Zhao, Jie; Pelletier, Jean-Pierre; Martel-Pelletier, Johanne; Di Battista, John A.
CORPORATE SOURCE: Department of Medicine, University of Montreal, Montreal, PQ, Can.
SOURCE: J. Cell. Biochem. (1998), 69(4), 392-413
CODEN: JCEBD5; ISSN: 0730-2312
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The involvement of serine/threonine **protein** phosphatases in signaling pathways that control the expression of the cyclooxygenase-2 (COX-2) gene in human chondrocytes was examd. Okadaic acid (OKA), an **inhibitor** of **protein** phosphatases 1 (PP-1) and 2A (PP-2A), induced a delayed, time-dependent increase in the rate of COX-2 gene transcription (runoff assay) resulting in increased steady-state mRNA levels and enzyme synthesis. The latter response was dose dependent over a narrow range of 1-30 nmol/L with declining expression and synthesis of COX-2 at higher concns. due to cell toxicity. The delayed increase in COX-2 mRNA expression was accompanied by the induction of the proto-oncogenes c-jun, junB, junD, and c-fos (but not FosB or Fra-1). Increased phosphorylation of CREB-1/ATF-1 transcription factors was obsd. beginning at 4 h and reached a zenith at 8 h. Gel-shift anal. confirmed the up-regulation of AP-1 and CRE nuclear binding **proteins**, though there was little or no OKA-induced nuclear **protein** binding to SP-1, **AP-2**, NF-KB or NF-IL-6 regulatory elements. OKA-induced nuclear **protein** binding to 32P-CRE oligonucleotides was abrogated by a **pharmacol. inhibitor** of **protein** kinase A (PKA), KT-5720; the latter compd. also **inhibited** OKA-induced COX-2 enzyme synthesis. Calphostin C (CalC), an **inhibitor** of PKC isoenzymes, had little effect in this regard. **Inhibition** of 32P-CRE binding was also obsd. in the presence of an antibody to CREB-binding **protein** (265-kDa CBP), an integrator and coactivator of cAMP-responsive genes. The binding to 32P-CRE was unaffected in the presence of excess radioinert AP-1 and COX-2 NF-IL-6 oligonucleotides, although a COX-2 CRE-oligo competed very

efficiently. 32P-AP-1 consensus sequence binding was unaffected by incubation of chondrocytes with KT-5720 or CalC, but was dramatically diminished by excess radioinert AP-1 and CRE-COX-2 oligos. Supershift anal. in the presence of antibodies to c-Jun, c-Fos, JunD, and JunB suggested that AP-1 complexes were composed of c-Fos, JunB, and possibly c-Jun. OKA has no effect on total cellular PKC activity but caused a delayed time-dependent increase in total PKA activity and synthesis. OKA suppressed the activity of the MAP kinases, ERK1/2 in a time-dependent fashion, suggesting that the Raf-1/MEKK1/MEK1/ERK1,2 cascade was compromised by OKA treatment. By contrast, OKA caused a dramatic increase in SAPK/JNK expression and activity, indicative of an activation of MEKK1/JNKK/SAPK/JNK pathway. OKA stimulated a dose-dependent activation of CAT activity using transfected promoter-CAT constructs harboring the regulatory elements AP-1 (c-jun promoter) and CRE (CRE-tkCAT). We conclude that in primary phenotypically stable human chondrocytes, COX-2 gene expression may be controlled by crit. phosphatases that interact with phosphorylation dependent (e.g., MAP kinases:AP-1 PKA:CREB/ATF) signaling pathways. AP-1 and CREB/ATF families of transcription factors may be important substrates for PP-1/PP-2A in human chondrocytes.

L40 ANSWER 10 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:288651 HCAPLUS
DOCUMENT NUMBER: 129:63845
TITLE: Cloning, expression, **pharmacology** and tissue distribution of the mouse somatostatin receptor subtype 5
AUTHOR(S): Baumeister, Hans; Kreuzer, Oliver J.; Roosterman, Dirk; Schafer, Judith; Meyerhof, Wolfgang
CORPORATE SOURCE: Abteilung Molekulare Genetik, Deutsches Institut fur Ernahrungsforschung, Potsdam, D-14558, Germany
SOURCE: J. Neuroendocrinol. (1998), 10(4), 283-290
CODEN: JOUNE2; ISSN: 0953-8194
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The gene encoding the mouse somatostatin receptor subtype 5 has been isolated from a genomic library and the mRNA start point mapped to position -95 relative to the translational start codon. The promoter region is devoid of TATA and CAAT boxes but contains putative binding sites for AP-1, **AP-2** and SP1 and response elements for glucocorticoids (GRE) and phorbol esters (TRE). The encoded receptor **protein** with a predicted mol. wt. of 42.5 kDa is comprised of 385 amino acids and thus contains 22 and 21 amino acids more than rat and human counterparts. The extra amino acids are caused by another translational initiation codon located further upstream. In the region of overlap the mouse somatostatin receptor subtype 5 displays 96.7% sequence identity to the rat and 81.7% to the human homolog. Application of somatostatin-14 and -28 to human embryonic kidney cells expressing the recombinant receptor resulted in the **inhibition** of forskolin-stimulated adenylyl cyclase with comparable EC50 values. Consistent with the obsd. sequence relationship, the mouse somatostatin receptor subtype 5 displays a **pharmacol.** profile that resembles the rat homolog more closely than the human counterpart. MRNA for the mouse somatostatin type 5 receptor has been detected in pituitary, kidney, spleen and ovary and, to a lesser extent, in brain, stomach, intestine and thymus but was not obsd. in heart, pancreas and liver.

L40 ANSWER 11 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:236085 HCAPLUS
DOCUMENT NUMBER: 129:710
TITLE: Budesonide epimer R or dexamethasone selectively inhibit platelet-activating factor-induced or interleukin 1.beta.-induced DNA binding activity of cis-acting transcription factors and cyclooxygenase-2 gene expression in human epidermal keratinocytes
AUTHOR(S): Lukiw, Walter J.; Pelaez, Ricardo Palacios; Martinez,

Jorge; Bazan, Nicolas G.
CORPORATE SOURCE: Louisiana State University Medical Center, Neuroscience Center of Excellence and Department of Ophthalmology, School of Medicine, New Orleans, LA, 70112-2272, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1998), 95(7), 3914-3919
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To further understand the mol. mechanism of glucocorticoid action on gene expression, DNA-binding activities of the cis-acting transcription factors activator **protein** 1 (AP1), **AP2**, Egr1 (zif268), NF-.kappa.B, the signal transducers and activators of transcription **proteins** gamma interferon activation site (GAS), Sis-inducible element, and the TATA binding **protein** transcription factor II D (TFIID) were examd. in human epidermal keratinocytes. The cytokine interleukin 1.beta. (IL-1.beta.) and platelet-activating factor (PAF), both potent mediators of inflammation, were used as triggers for gene expression. Budesonide epimer R (BUDeR) and dexamethasone (DEX) were studied as potential antagonists. BUDeR or DEX before IL-1.beta.- or PAF-mediated gene induction elicited strong **inhibition** of AP1-, GAS-, and in particular NF-.kappa.B-DNA binding ($P < 0.001$, ANOVA). Only small effects were noted on **AP2**, Egr1 (zif268), and Sis-inducible element-DNA binding ($P > 0.05$). No significant effect was noted on the basal transcription factor TFIID recognition of TATA-contg. core promoter sequences ($P > 0.68$). To test the hypothesis that changing cis-acting transcription factor binding activity may be involved in inflammatory-response related gene transcription, RNA message abundance for human cycloxygenase (COX)-1 and -2 (E.C.1.14.99.1) was assessed in parallel by using reverse transcription-PCR. Although the COX-1 gene was found to be expressed at constitutively low levels, the TATA-contg. COX-2 gene, which contains AP1-like, GAS, and NF-.kappa.B DNA-binding sites in its immediate promoter, was found to be strongly induced by IL-1.beta. or PAF ($P < 0.001$). BUDeR and DEX both suppressed COX-2 RNA message generation; however, no correlation was assocd. with TFIID-DNA binding. These results suggest that on stimulation by mediators of inflammation, although the basal transcription machinery remains intact, modulation of cis-activating transcription factor AP1, GAS, and NF-.kappa.B-DNA binding by the glucocorticoids BUDeR and DEX play important regulatory roles in the extent of specific promoter activation and hence the expression of key genes involved in the inflammatory response.

L40 ANSWER 12 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:757918 HCAPLUS
DOCUMENT NUMBER: 128:97557
TITLE: 3',5'-Cyclic adenosine monophosphate-response sequences of the uncoupling protein gene are sequentially recruited during darglitazone-induced brown adipocyte differentiation
AUTHOR(S): Rabelo, Roberio; Camirand, Anne; Silva, J. Enrique
CORPORATE SOURCE: Div. Endocrinol., Jewish Gen. Hosp., Lady Davis Inst. Medical Res., McGill Univ., Montreal, PQ, H3T 1E2, Can.
SOURCE: Endocrinology (1997), 138(12), 5325-5332
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Uncoupling **protein**-1 (UCP) is uniquely expressed in brown adipose tissue (BAT) and is essential to the thermogenic function of this tissue. The UCP gene is under the control of norepinephrine (NE) via cAMP. However, the precise delineation of the cAMP response sequences and mechanisms whereby cAMP stimulate the gene have remained elusive. A BAT tumor cell line, HIB-1B, can be differentiated into UCP-expressing brown

adipocytes. We report here that when these cells are differentiated with a std. differentiation protocol including insulin, T3, hydrocortisone, IBMX, and indomethacin (std. differentiation, StD), cAMP stimulation of the rat UCP gene is largely mediated by an upstream 90-bp sequence-2399/2490 (R90) with a lesser contribution of a downstream sequence-57/+114 (dnCRS). This latter is functional also in non-BAT cells, whereas the cAMP response sequence contained in R90 (upCRS) is BAT-specific. Thiazolidinediones (TZD) are a new group of **drugs** known to increase sensitivity to insulin and, more recently, to induce adipocyte differentiation (adipogenesis) via PPAR.gamma.. A TZD, darglitazone (Darg), can rapidly induce differentiation of HIB-1B cells, as judged by the expression of the adipocyte lipid binding **protein** (**aP2**), lipoprotein lipase (LPL), uncoupling **protein** (UCP) and .beta.3-adrenergic receptors. UCP mRNA responsive to NE is evidenced as early as one day after exposure to Darg. While UCP-CAT vectors (+114/-3673 bp of rat UCP gene) are barely responsive to NE in HIB-1B preadipocytes, both Darg and StD markedly enhance NE responsiveness of such constructs. However, by 3 days of exposure to Darg, the responses were less vigorous than in StD cells (4- to 10-fold vs. 20- to 50-fold), and the deletion of R90 did not affect the response to NE in Darg-differentiated cells, whereas this deletion caused a 75% redn. in StD cells. Prolongation of Darg exposure to 5-7 days resulted in greater response of UCP mRNA to NE and 50-80% **inhibition** of the response of UCP-CAT vectors by the deletion of R90. Thus, Darg-induced differentiation of HIB-1B cells suggests that the NE-dependent expression of the UCP gene takes place in a step-wise manner: first, the gene is "enabled", as no UCP mRNA is detected in HIB-1B preadipocytes; thereafter and transiently, the response of the gene to NE is sustained by dnCRS; finally, as differentiation progresses, a cell-specific and more powerful cis-acting sequence, upCRS, is recruited, accounting in the fully differentiated cell for most of the response to NE. These results also suggest that TZDs might increase energy expenditure by inducing terminal differentiation of BAT, and that these **drugs** may be useful in the differential cloning of the factors involved in the recruitment of the BAT specific cAMP response sequence.

L40 ANSWER 13 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:652920 HCAPLUS
DOCUMENT NUMBER: 127:344334
TITLE: ADP-ribosylation factor 6 regulates a novel plasma membrane recycling pathway
AUTHOR(S): Radhakrishna, Harish; Donaldson, Julie G.
CORPORATE SOURCE: Laboratory of Cell Biology, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, 20892, USA
SOURCE: J. Cell Biol. (1997), 139(1), 49-61
CODEN: JCLBA3; ISSN: 0021-9525
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB ADP-ribosylation factor (ARF) 6 localizes to the plasma membrane (PM) in its GTP state and to a tubulovesicular compartment in its GDP state in HeLa cells that express wild-type or mutant forms of this GTPase. Aluminum fluoride (AlF) treatment of ARF6-transfected cells redistributes ARF6 to the PM and stimulates the formation of actin-rich surface protrusions. Here we show that cytochalasin D (CD) treatment **inhibited** formation of the AlF-induced protrusions and shifted the distribution of ARF6 to a tubular membrane compartment emanating from the juxtanuclear region of cells, which resembled the compartment where the GTP-binding defective mutant of ARF6 localized. This membrane compartment was distinct from transferrin-pos. endosomes, could be detected in the absence of ARF6 overexpression or CD treatment, and was accessible to loading by PM **proteins** lacking clathrin/**AP-2** cytoplasmic targeting sequences, such as the IL-2 receptor .alpha. subunit Tac. ARF6 and surface Tac moved into this compartment and back out to the PM in the absence of **pharmacol**. treatment. Whereas AlF

treatment blocked internalization, CD treatment blocked the recycling of wild-type ARF6 and Tac back to the PM; these blocks were mimicked by expression of ARF6 mutants Q67L and T27N, which were predicted to be in either the GTP- or GDP-bound state, resp. Thus, the ARF6 GTP cycle regulates this membrane traffic pathway. The delivery of ARF6 and membrane to defined sites along the PM may provide components necessary for remodeling the cell surface and the underlying actin cytoskeleton.

L40 ANSWER 14 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:373765 HCAPLUS
DOCUMENT NUMBER: 127:75634
TITLE: Activation of NF-.kappa.B by antineoplastic agents. Role of protein kinase C
AUTHOR(S): Das, Kumuda C.; White, Carl W.
CORPORATE SOURCE: Dep. Pediatrics, National Jewish Medical Res. Center, Denver, CO, 80206, USA
SOURCE: J. Biol. Chem. (1997), 272(23), 14914-14920
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Paclitaxel can induce tumor necrosis factor (TNF) and interleukin-1 gene expression, similar to lipopolysaccharides. Since lipopolysaccharide-induced expression of TNF is related to activation of NF-.kappa.B, the authors detd. whether NF-.kappa.B could be activated by paclitaxel. In the human lung adenocarcinoma cell line A549, paclitaxel activated NF-.kappa.B in a dose-dependent manner with maximal activation after 2-4 h. Since paclitaxel could upregulated TNF and interleukin-1 secretion and subsequent NF-.kappa.B activation could be caused by these cytokines, the effect of two other groups of anticancer **drugs** including vinca alkaloids (vinblastine and vincristine) and anthracyclines (daunomycin and doxorubicin), neither of which induce TNF or interleukin-1 gene expression, were examd. Like paclitaxel, vinblastine, vincristine, daunomycin, and doxorubicin each caused activation of NF-.kappa.B. Therefore, it is unlikely that activation of NF-.kappa.B caused by these agents or by paclitaxel is mediated via cytokine up-regulation. Furthermore, actinomycin D and cycloheximide, **inhibitors** of transcription and translation, resp., did not **inhibit** paclitaxel-induced NF-.kappa.B activation. Several other transcription factors such as AP-1, **AP-2**, CREB, SP-1, or TFIID were not activated by antineoplastic agents, demonstrating specificity of NF-.kappa.B activation. The involvement of both subunits in the NF-.kappa.B DNA binding complex was demonstrated by its abrogation by anti-p65 and by supershift by anti-p50 antibodies. Since **protein** phosphorylation is implicated in the activation of NF-.kappa.B, the effect of anticancer **drugs** on **protein** kinase C activity was measured. Vincristine, daunomycin, and paclitaxel significantly increased **protein** kinase C activity, and vinblastine and doxorubicin caused similar trends. Following treatment with antineoplastics (1-4 h), cytoplasmic I.kappa.B.alpha. degrdn. occurred concomitantly with translocation of p65 to the nucleus. Specific **protein** kinase C **inhibitors** (bisindolylmaleimide (GF109203X) and calphostin C) blocked the activation of NF-.kappa.B by each compd. Hence, **protein** kinase C activation may contribute to NF-.kappa.B activation by antineoplastic agents.

L40 ANSWER 15 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:746890 HCAPLUS
DOCUMENT NUMBER: 126:72078
TITLE: Activation of transcription factor AP-2 mediates UVA radiation- and singlet oxygen-induced expression of the human intercellular adhesion molecule 1 gene
AUTHOR(S): Grether-Beck, Susanne; Olaizola-Horn, Sylvia; Schmitt, Heidi; Grewe, Markus; Jahnke, Andreas; Johnson, Judith P.; Briviba, Karlis; Sies, Helmut; Krutmann, Jean

CORPORATE SOURCE: Clinical Exp. Photodermatol., Dep. Dermatol., Duesseldorf, D-40225, Germany
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1996), 93(25), 14586-14591
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB UVA radiation is the major component of the UV solar spectrum that reaches the earth, and the **therapeutic** application of UVA radiation is increasing in **medicine**. Anal. of the cellular effects of UVA radiation has revealed that exposure of human cells to UVA radiation at physiol. doses leads to increased gene expression and that this UVA response is primarily mediated through the generation of singlet oxygen. In this study, the mechanisms by which UVA radiation induces transcriptional activation of the human intercellular adhesion mol. 1 (ICAM-1) were examd. UVA radiation was capable of inducing activation of the human ICAM-1 promoter and increasing ICAM-1 mRNA and **protein** expression. These UVA radiation effects were **inhibited** by singlet oxygen quenchers, augmented by enhancement of singlet oxygen life-time, and mimicked in unirradiated cells by a singlet oxygen-generating system. UVA radiation as well as singlet oxygen-induced ICAM-1 promoter activation required activation of the transcription factor **AP-2**. Accordingly, both stimuli activated **AP-2**, and deletion of the putative **AP-2**-binding site abrogated ICAM-1 promoter activation in this system. This study identified the **AP-2** site as the UVA radiation- and singlet oxygen-responsive element of the human ICAM-1 gene. The capacity of UVA radiation and/or singlet oxygen to induce human gene expression through activation of **AP-2** indicates a previously unrecognized role of this transcription factor in the mammalian stress response.

L40 ANSWER 16 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:828260 HCAPLUS
DOCUMENT NUMBER: 123:275347
TITLE: Calpain inhibitor-induced apoptosis in human prostate adenocarcinoma cells
AUTHOR(S): Zhu, Wen; Murtha, Patricia E.; Young, Charles Y. F.
CORPORATE SOURCE: Dep. Urology Biochem. Mol. Biol., Mayo Clinic/Found., Rochester, MN, 55905, USA
SOURCE: Biochem. Biophys. Res. Commun. (1995), 214(3), 1130-7
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Although it has been shown that calpains may play a pos. role in causing apoptosis of T cells, we report here that, on the contrary, the **inhibition** of calpain-like activities can induce apoptosis in human prostate cancer cells. Two calpain **inhibitors** were used to test growth response on prostate cancer cells and showed remarkable cytotoxicity. The cytotoxicity was due to apoptosis as judged by large genomic DNA fragmentation, chromatin condensation and nuclear fragmentation. Furthermore, using gel band shift assays we have demonstrated that calpain **inhibitor** 1 causes a prolonged elevation of AP-1 **protein** activity in human prostate cancer cells. The elevation of AP-1 activity appears to be specific, because calpain **inhibitor** 1 only stimulates AP-1 but not **AP-2** and SP-1 activities. We postulate that the sustained increase in AP-1 activity may be involved in apoptosis induced in prostate cells by calpain **inhibitors**. Our study thus suggests that calpain-like activity may be a potentially **therapeutic** target for cancer.

L40 ANSWER 17 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:562723 HCAPLUS
DOCUMENT NUMBER: 123:515
TITLE: Inhibition of AP-1 binding and transcription by gold

and selenium involving conserved cysteine residues in Jun and Fos
AUTHOR(S): Handel, Malcolm L.; Watts, Colin K. W.; DeFazio, Anna; Day, Richard O.; Sutherland, Robert L.
CORPORATE SOURCE: Cancer Biology Division, Garvan Institute of Medical Research, Sydney, 2010, Austria
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1995), 92(10), 4497-501
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Gold(I) salts and selenite, which have diverse **therapeutic** and biol. effects, are noted for their reactivity with thiols. Since the binding of Jun-Jun and Jun-Fos dimers to the AP-1 DNA binding site is regulated in vitro by a redox process involving conserved cysteine residues, we hypothesized that some of the biol. actions of gold and selenium are mediated via these residues. In electrophoretic mobility-shift analyses, AP-1 DNA binding was **inhibited** by gold(I) thiolates and selenite, with 50% **inhibition** occurring at approx. 5 .mu.M and 1 .mu.M, resp. Thiomalic acid had no effect in the absence of gold(I), and other metal ions **inhibited** at higher concns., in a rank order correlating with their thiol binding affinities. Cysteine-to-serine mutants demonstrated that these effects of gold(I) and selenite require Cys2172 and Cys154 in the DNA-binding domains of Jun and Fos, resp. Gold(I) thiolates and selenite did not **inhibit** nonspecific **protein** binding to the AP-1 site and were at least an order of magnitude less potent as **inhibitors** of sequence-specific binding to the **AP-2**, TFIID, or NF1 sites compared with the AP-1 site. In addn., 10 .mu.M gold(I) or 10 .mu.M selenite **inhibited** expression of an AP-1-dependent reporter gene, but not an **AP-2**-dependent reporter gene. These data suggest a mechanism regulating transcription factor activity by inorg. ions which may contribute to the known antiarthritic action of gold and cancer chemoprevention by selenium.

L40 ANSWER 18 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:646753 HCAPLUS
DOCUMENT NUMBER: 119:246753
TITLE: Mis-assembly of clathrin lattices on endosomes reveals a regulatory switch for coated pit formation
AUTHOR(S): Wang, Li Hsien; Rothberg, Karen G.; Anderson, Richard G. W.
CORPORATE SOURCE: Southwest. Med. Cent., Univ. Texas, Dallas, TX, 75235, USA
SOURCE: J. Cell Biol. (1993), 123(5), 1107-18
CODEN: JCLBA3; ISSN: 0021-9525
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The clathrin-coated pit lattice is held onto the plasma membrane by an integral membrane **protein** that binds the clathrin **AP-2** subunit with high affinity. In vitro studies have suggested that this **protein** controls the assembly of the pit because membrane bound **AP-2** is required for lattice assembly. If so, the **AP-2** binding site must be a resident **protein** of the coated pit and recycle with other receptors that enter cells through this pathway. Proper recycling, however, would require the switching off of **AP-2** binding to allow the binding site to travel through the endocytic pathway unencumbered. Evidence for this hypothesis has been revealed by the cationic amphiphilic class of **drugs** (CAD), which have previously been found to **inhibit** receptor recycling. Incubation of human fibroblasts in the presence of these **drugs** caused clathrin lattices to assemble on endosomal membranes and at the same time prevented coated pit assembly at the cell surface. These effects suggest that CADs reverse an on/off switch that controls **AP-2** binding to membranes. The authors conclude that cells have a mechanism for switching on and off

AP-2 binding during the endocytic cycle.

L40 ANSWER 19 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:146156 HCAPLUS
DOCUMENT NUMBER: 116:146156
TITLE: Antifungal osmotin-like proteins from plants
PATENT ASSIGNEE(S): Mogen International N. V., Neth.
SOURCE: Neth. Appl., 16 pp.
CODEN: NAXXAN
DOCUMENT TYPE: Patent
LANGUAGE: Dutch
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
NL 9001294	A	19920102	NL 1990-1294	19900607

AB Plant **proteins** showing >80% homol. with the amino acid sequence of tobacco osmotin and a basic pI, isolated from Solanaceae, Leguminosae, Gramineae, Umbelliferae, or cotton, are growth and sporulation **inhibitors** for fungi and are useful as fungicides on plants and as preservatives for food, **drugs**, cosmetics, etc. Thus, osmotin **AP20** was isolated from tobacco leaves by chromatog. on Sephadex G25, S-Sepharose Fast Flow, and Ph Superose HR 5/5. Purified **AP20** provided 100% growth **inhibition** of Phytophthora infestans, at 10 .mu.g/mL, in vitro.

L40 ANSWER 20 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:35394 HCAPLUS
DOCUMENT NUMBER: 116:35394
TITLE: Genomic sequence and expression of a cloned human carbonyl reductase gene with daunorubicin reductase activity
AUTHOR(S): Forrest, Gerald L.; Akman, Steve; Doroshow, James; Rivera, Hector; Kaplan, William D.
CORPORATE SOURCE: Dep. Biol., Beckman Res. Inst. City of Hope, Duarte, CA, 91010, USA
SOURCE: Mol. Pharmacol. (1991), 40(4), 502-7
CODEN: MOPMA3; ISSN: 0026-895X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Carbonyl reductase (NADPH:secondary-alc. oxidoreductase; EC 1.1.1.184), a widely distributed NAPDPH-dependent enzyme considered as both an aldo-keto reductase and a quinone reductase, was cloned from a human liver genomic library and transiently expressed in COS7 cells. The gene contains 3142 bases comprising 3 exons and 2 introns. The absence of a CAAT and TATA box and the presence of a GC-rich island are characteristic of many housekeeping genes. Transient expression of the genomic gene in CO7 cells using an expression vector contg. an SV40 origin of replication resulted in a >50-fold increase in both menadione reductase activity and daunorubicin reductase activity, suggesting that both activities are derived from the same enzyme. Carbonyl reductase mRNA levels reflected enzyme activity levels in the transfected cells. Other parameters, such as pH profile, cofactor requirements, substrates, and **inhibitors** , were similar to those of carbonyl reductase purified by other investigators. Potential regulatory elements with consensus sequences for 2 GC boxes and the transcriptional activator **protein AP -2** were present upstream of the transcriptional start site. Although the precise role of carbonyl reductase is unknown, the enzyme is involved in **drug** metab. and in the redn. of activated carbonyl compds. Its ability to act as a quinone reductase also implies a potential to modulate oxygen free radicals.

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L3              STR
L5           54 SEA FILE=REGISTRY SSS FUL L3
L6              STR
L7            5 SEA FILE=REGISTRY SUB=L5 SSS FUL L6
L8            5 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7
L10          49 SEA FILE=REGISTRY ABB=ON  PLU=ON  L5 NOT L7
L11           1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L10 NOT L8
L13       13312 SEA FILE=REGISTRY ABB=ON  PLU=ON  OXAZOLE?/CN
L14         173 SEA FILE=REGISTRY ABB=ON  PLU=ON  AP2?
L15       31521 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L13 OR ?OXAZOLE?
L16        2486 SEA FILE=HCAPLUS ABB=ON  PLU=ON  AP2? OR AP(W)2 OR L14
L17           3 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L16 AND L15
L18           1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L17 NOT (L8 OR L11)
L19          98 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L16(L)(?DIABET? OR ?OBES? OR
                 ?HYPERGLYCE? OR ?HYPERINSULIN? OR ?HYPERTRIGLY? OR ?HYPERFATTY?
                  OR ?HYPERGLYCEROL?)
L20         362 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L16(L)(?MEDIC? OR ?PHARM? OR
                 ?DRUG? OR ?THERAP? OR ?TREAT?)
L21          33 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L19 AND L20
L22          30 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L21 NOT (L8 OR L11 OR L18)
L23         443 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L16(L)INHIBIT?
L25          18 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L23 AND L19
L26           7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L25 NOT (L8 OR L11 OR L18 OR
                 L22)
L33        1349 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L16(L)PROTEIN
L34         289 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L33 AND L23
L39          24 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L34 AND (?MEDIC? OR ?PHARM?
                 OR ?DRUG? OR ?THERAP?)
L40          20 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L39 NOT (L8 OR L11 OR L18 OR
                 L22 OR L26)
L41          69 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ADIPOCYTE(W)PROTEIN(W)2
L44          16 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L41 AND (?DIABET? OR ?OBES?
                 OR ?HYPERGLYCE? OR ?HYPERINSULIN? OR ?HYPERTRIGLY? OR ?HYPERFAT
                 TY? OR ?HYPERGLYCEROL?)
L45           8 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L44 NOT (L8 OR L11 OR L18 OR
                 L22 OR L26)
L46           8 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L45 NOT L40


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=> d ibib abs hitrn l46 1-8


L46  ANSWER 1 OF 8  HCAPLUS  COPYRIGHT 2001 ACS
ACCESSION NUMBER:         2000:603847  HCAPLUS
DOCUMENT NUMBER:          133:294896
TITLE:                    Improved glucose and lipid metabolism in genetically
                         obese mice lacking aP2
AUTHOR(S):                Uysal, K. Teoman; Scheja, Ludger; Wiesbrock, Sarah M.;
                          Bonner-Weir, Susan; Hotamisligil, Gokhan S.
CORPORATE SOURCE:         Division of Biological Sciences and Department of
                          Nutrition, Harvard School of Public Health, Boston,
                          MA, 02115, USA
SOURCE:                   Endocrinology (2000), 141(9), 3388-3396
                          CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER:                Endocrine Society
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   Adipocyte fatty acid-binding protein, aP2, is a member of the
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intracellular fatty acid binding protein family. Previously, studies have shown increased insulin sensitivity in aP2-deficient mice with dietary **obesity**. Here, we asked whether aP2-related alterations in lipolytic response and insulin prodn. are features of **obesity** -induced insulin resistance and investigated the effects of aP2-deficiency on glucose homeostasis and lipid metab. in ob/ob mice, a model of extreme **obesity** ob/ob mice homozygous for the aP2 null allele (ob/ob-aP2-/-) became more **obese** than ob/ob mice as indicated by significantly increased body wt. and fat pad size but unaltered body length. However, despite their extreme adiposity, ob/ob-aP2-/- animals were more insulin-sensitive compared with ob/ob controls, as demonstrated by significantly lower plasma glucose and insulin levels and better performance in both insulin and glucose tolerance tests. These animals also showed improvements in dyslipidemia and had lower plasma triglyceride and cholesterol levels. Lipolytic response to .beta.-adrenergic stimulation and lipolysis-assocd. insulin secretion was significantly reduced in ob/ob-aP2-/- mice. Interestingly, glucose-stimulated insulin secretion, while virtually abolished in ob/ob controls, was significantly improved in ob/ob-aP2-/- animals. There were no apparent morphol. differences in the structure or size of the pancreatic islets between genotypes. Taken together, the data indicate that in **obesity**, aP2-deficiency not only improves peripheral insulin resistance but also preserves pancreatic .beta. cell function and has beneficial effects on lipid metab.

REFERENCE COUNT: 41

REFERENCE(S):
(1) Bernlohr, D; Biochem Biophys Res Commun 1985, V132, P850 HCAPLUS
(2) Bloom, J; J Med Chem 1992, V35, P3081 HCAPLUS
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(4) Bruning, J; Mol Cell 1998, V2, P559 HCAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L46 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:493702 HCAPLUS

DOCUMENT NUMBER: 133:99541

TITLE: Methods of screening protease inhibitors, of inducing mice susceptible to HIV protease inhibitor-induced dyslipidemia, and genes associated therewith

INVENTOR(S): Lenhard, James Martin

PATENT ASSIGNEE(S): Glaxo Group Limited, UK

SOURCE: PCT Int. Appl., 79 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000042211	A1	20000720	WO 2000-US1205	20000119

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:		
US 1999-116300	19990119	
US 1999-137620	19990604	
US 1999-146309	19990727	

AB The invention relates generally to the side effects caused by retroviral therapies, including protease inhibitors, nucleoside reverse transcriptase

inhibitors, and non-nucleoside reverse transcriptase inhibitors. Specifically, methods are provided for screening a protease inhibitor for its capacity to affect symptoms or clin. conditions assocd. with lipodystrophy or dyslipidemia and related metabolic disorders, such as metabolic syndrome X, **obesity**, cardiovascular disorders, and impaired glucose tolerance in **diabetes**, in a patient.

REFERENCE COUNT: 4

REFERENCE(S):
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(2) Carr, A; Lancet 1998, V351, P1881 HCAPLUS
(3) Shaw, A; International Journal of STD & AIDS 1998, V9, P595 MEDLINE
(4) Shimomura, I; Genes & Development 1998, V12, P3182 HCAPLUS

L46 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:644010 HCAPLUS
DOCUMENT NUMBER: 131:335295
TITLE: Altered insulin secretion associated with reduced lipolytic efficiency in aP2-/- mice
AUTHOR(S): Scheja, Ludger; Makowski, Liza; Uysal, K. Teoman; Wiesbrock, Sarah M.; Shimshek, Derya R.; Meyers, Daniel S.; Morgan, Maureen; Parker, Rex A.; Hotamisligil, Gokhan S.
CORPORATE SOURCE: Division of Biological Sciences and Department of Nutrition, Harvard School of Public Health, Boston, MA, 02115, USA
SOURCE: Diabetes (1999), 48(10), 1987-1994
CODEN: DIAEAZ; ISSN: 0012-1797
PUBLISHER: American Diabetes Association
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recent studies have shown that genetic deficiency of the adipocyte fatty acid-binding protein (aP2) results in minor alterations of plasma lipids and adipocyte development but provides significant protection from dietary **obesity**-induced **hyperinsulinemia** and insulin resistance. To identify potential mechanisms responsible for this phenotype, we examd. lipolysis and insulin secretion in aP2-/- mice. .beta.-Adrenergic stimulation resulted in a blunted rise of blood glycerol levels in aP2-/- compared with aP2+/+ mice, suggesting diminished lipolysis in aP2-/- adipocytes. Confirming this, primary adipocytes isolated from aP2-/- mice showed attenuated glycerol and free fatty acid (FFA) release in response to dibutyryl cAMP. The decreased lipolytic response seen in the aP2-/- mice was not assocd. with altered expression levels of hormone-sensitive lipase or perilipin. The acute insulin secretory response to .beta.-adrenergic stimulation was also profoundly suppressed in aP2-/- mice despite comparable total concns. and only minor changes in the compn. of systemic FFAs. To address whether levels of specific fatty acids are different in aP2-/- mice, the plasma FFA profile after .beta.-adrenergic stimulation was detd. Significant redn. in both stearic and cis-11-eicoseneic acids and an increase in palmitoleic acid were obsd. The response of aP2-/- mice to other insulin secretagogues such as arginine and glyburide was similar to that of aP2+/+ mice, arguing against generally impaired function of pancreatic .beta.-cells. Finally, no aP2 expression was detected in isolated pancreatic islet cells. These results provide support for the existence of an adipo-pancreatic axis, the proper action of which relies on the presence of aP2. Consequently, aP2's role in the pathogenesis of type 2 **diabetes** might involve regulation of both **hyperinsulinemia** and insulin resistance through its impact on both lipolysis and insulin secretion.

REFERENCE COUNT: 68

REFERENCE(S):
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(2) Bernlohr, D; Annu Rev Nutr 1997, V17, P277 HCAPLUS
(3) Bernlohr, D; Biochem Biophys Res Commun 1985, V132, P850 HCAPLUS
(4) Bloom, J; J Med Chem 1992, V35, P3081 HCAPLUS
(5) Boden, G; Diabetes 1997, V46, P3 HCAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L46 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:467835 HCAPLUS
DOCUMENT NUMBER: 131:269967
TITLE: PPAR.gamma. activation induces the expression of the adipocyte fatty acid binding protein gene in human monocytes
AUTHOR(S): Pelton, Patricia D.; Zhou, Lubing; Demarest, Keith T.; Burris, Thomas P.
CORPORATE SOURCE: Department of Drug Discovery, Endocrine Therapeutics, R. W. Johnson Pharmaceutical Research Institute, Raritan, NJ, 08869, USA
SOURCE: Biochem. Biophys. Res. Commun. (1999), 261(2), 456-458
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The peroxisome-proliferator activated receptor gamma (PPAR.gamma.), a member of the nuclear receptor superfamily of ligand activated transcription factors, plays a key role in the anti-**diabetic** actions of the thiazolidinediones (TZDs). PPAR.gamma. induces the expression of many genes involved in lipid anabolism, including the adipocyte fatty acid binding protein (aP2), and is a key regulator of adipocyte differentiation. PPAR.gamma. is also expressed in hematopoietic cells and is up-regulated in activated monocytes/macrophages. Activation of PPAR.gamma. may play a role in the induction of differentiation of macrophages to foam cells that are assocd. with atherosclerotic lesions. We report that both natural and synthetic PPAR.gamma. agonists induce time- and dose-dependent increases in aP2 mRNA in both primary human monocytes and the monocytic cell line, THP-1. PPAR.gamma. activation may play a role in monocyte differentiation and function analogous to its well-characterized role in adipocytes. (c) 1999 Academic Press.
REFERENCE COUNT: 19
REFERENCE(S): (1) Boyum, A; J Clin Lab Invest 1968, V21(97), P77 HCAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L46 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:414960 HCAPLUS
DOCUMENT NUMBER: 131:226573
TITLE: Fat storage capacity in growth-selected and control mouse lines is associated with line-specific gene expression and plasma hormone levels
AUTHOR(S): Timtchenko, D.; Kratzsch, J.; Sauerwein, H.; Wegner, J.; Souffrant, W. B.; Schwerin, M.; Brockmann, G. A.
CORPORATE SOURCE: Research Institute for the Biology of Farm Animals, Dummerstorf, D-18196, Germany
SOURCE: Int. J. Obes. (1999), 23(6), 586-594
CODEN: IJOBDP; ISSN: 0307-0565
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB For a detailed understanding of the complex traits growth and fat storage, a dissection into single genetic entities is mandatory. Therefore, blood plasma concns. of hormones and the expression of selected genes were measured in extremely differentiated mouse lines. Genes were selected as candidates which might influence the complex traits body wt. and fat accumulation, and which are located in chromosomal regions recently identified to affect trait differences between the lines. The mouse lines

were selected for high body wt. (DU6), high carcass protein content (DU6P) and unselected controls (DUKs). In the selected lines DU6 and DU6P, mean body wts. at the age of six weeks were about twice as high as the DUKs, whereas total fat wt. was increased 2.2-fold in DU6 mice compared to DU6P and 3.2-fold in comparison to DUKs. Blood plasma concns. of insulin-like growth factor 1 (IGF-1), growth hormone (GH), insulin and leptin, were measured in all lines at three weeks and at six weeks of age. Expression patterns of the genes encoding growth hormone (Gh), insulin-like growth factor 1 (Igf1), lipoprotein lipase (Lpl), glycerolphosphate dehydrogenase 1 (GDC-1), and **adipocyte protein** 2 (Ap2)
were analyzed by Northern blot hybridization. In line DU6, highly significant increased concns. of insulin and leptin were obsd. at six weeks of age; at this stage, IGF-1 concns. were elevated in the two selected lines compared to controls with maximal concns. of IGF-1 and GH in DU6P. The amt. of mRNA for GH in the pituitary gland, for Igf1 in the liver and for LPL in epididymal fat tissue was significantly elevated in the two selected lines compared to controls at the age of three weeks, but not at six weeks. IGF-1 and GDC-1 mRNA concns. were significantly higher in the DU6 mice than in the DU6P ($P < 0.01$) and the DUKs ($P < 0.001$) mice examd. at both ages. The results prove line-specific concns. of the analyzed hormones and the transcription amts. of Gh, Igf1, GDC-1 and Lpl. The measured differences are either direct genetic effects or secondary changes, resulting from different food consumption.

REFERENCE COUNT: 47
REFERENCE(S):
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(3) Antras, J; Mol Cell Endocrinol 1991, V82, P183 HCAPLUS
(4) Bang, P; Endocrinolo 1995, V136, P816 HCAPLUS
(5) Bhandari, B; Mol Cell Endocrinol 1991, V76, P71 HCAPLUS
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L46 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:190162 HCAPLUS
DOCUMENT NUMBER: 128:306817
TITLE: Induction of the nuclear orphan receptor ROR.gamma. during adipocyte differentiation of D1 and 3T3-L1 cells
AUTHOR(S): Austin, Stephen; Medvedev, Alexander; Yan, Zhong-Hua; Adachi, Hiroshi; Hirose, Takahisa; Jetten, Anton M.
CORPORATE SOURCE: Cell Biology Section, Laboratory of Pulmonary Pathobiology, National Institute of Environmental Health Sciences, NIH, Research Triangle Park, NC, 27709, USA
SOURCE: Cell Growth Differ. (1998), 9(3), 267-276
CODEN: CGDIE7; ISSN: 1044-9523
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Here, we analyzed the expression of the three members of the retinoid-like orphan receptor (ROR) nuclear receptor subfamily during adipocyte differentiation. ROR.alpha. and ROR.gamma. mRNA were up-regulated during adipocyte differentiation in preadipocyte D1 and 3T3-L1 cells, whereas ROR.beta. mRNA could not be detected. The induction of ROR.alpha. and ROR.gamma. mRNA succeeded the induction of peroxisome proliferator-activated receptor .gamma. (PPAR.gamma.) and CCAAT/enhancer binding protein .alpha. and occurred at a similar time interval as did the increase in aP2 and lipoprotein lipase mRNA. Like the expression of PPAR.gamma. and aP2, the induction of ROR.gamma. mRNA was repressed by tumor necrosis factor .alpha. and transforming growth factor .beta.. The induction of adipogenesis by prostaglandin D2 and two thiazolidinediones in the multipotent stem cells C3H10T1/2 was also accompanied by an induction in ROR.gamma. mRNA. In contrast to parental cells, clofibrate induces adipogenesis and ROR.alpha. and ROR.gamma. mRNA in BALB/c3T3 cells that ectopically express PPAR.gamma.. ROR.gamma. mediates its effect on

transcription through specific response elements. Cotransfection of ROR.alpha. or ROR.gamma. and (ROR.gamma. response element)4-chloramphenicol acetyltransferase into preadipocyte D1 cells induced transactivation of chloramphenicol acetyltransferase about 100-fold, suggesting that ROR plays a role in the regulation of gene expression in adipocytes. The nuclear orphan receptor Rev-ErbA.alpha., which did not exhibit transactivation function, was able to inhibit transactivation by ROR.gamma. at two different levels. Our results show that ROR.gamma. is induced during adipocyte differentiation in D1 and 3T3-L1 cells and functions as an active transcription factor, suggesting a role for ROR.gamma. in the regulation of gene expression during this differentiation process.

L46 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:296943 HCAPLUS
DOCUMENT NUMBER: 122:96205
TITLE: Evidence for a common mechanism of action for fatty acids and thiazolidinedione **antidiabetic** agents on gene expression in preadipose cells
AUTHOR(S): Ibrahimi, Azeddine; Teboul, Lydia; Gaillard, Danielle; Amri, Ez-Zoubir; Alhaud, Gerard; Young, Paul; Cawthorne, Michael A.; Grimaldl, Paul A.
CORPORATE SOURCE: Fac. des Sciences, Univ. de Nice-Sophia, Nice, Fr.
SOURCE: Mol. Pharmacol. (1994), 46(6), 1070-6
CODEN: MOPMA3; ISSN: 0026-895X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In **diabetic** rodents, thiazolidinediones are able to improve the insulin sensitivity of target tissues and to reverse, at least partially, the **diabetic** state. The effects of these drugs on phenotypic expression in various tissues, including adipose tissue, are reported. Here, the authors report that a new thiazolidinedione compd., BRL 49653, exerts, in preadipose cells, potent effects on the expression of genes encoding proteins involved in fatty acid metab. These effects of BRL 49653 in Ob 1771 preadipose cells are similar, in terms of kinetics, reversibility, specificity of genes affected, and requirement for protein synthesis, to those already described for natural or nonmetabolizable fatty acids. Moreover, when used at submaximally effective concns., BRL 49653 and 2-bromopalmitate act in an additive manner to induce gene expression in preadipose cells, but this additivity of effects is lost when one of the compds. is used at a maximally effective concn. These observations, suggesting similar mechanisms of action for thiazolidinediones and fatty acids, are strongly supported by the demonstration that (i) both mols. activate, in a heterologous trans-activation assay, the same nuclear receptor of the steroid/thyroid hormone nuclear receptor superfamily and (ii) transfection of 3T3-C2 fibroblasts with an expression vector for this nuclear receptor confers thiazolidinedione inducibility of adipocyte lipid-binding protein gene expression.

L46 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:647123 HCAPLUS
DOCUMENT NUMBER: 119:247123
TITLE: Expression of the adipocyte fatty acid-binding protein in streptozotocin-**diabetes**: effects of insulin deficiency and supplementation
AUTHOR(S): Meli, Samir A.; Abumrad, Nada A.
CORPORATE SOURCE: Sch. Med., Vanderbilt Univ., Nashville, TN, 37232, USA
SOURCE: J. Lipid Res. (1993), 34(9), 1527-34
CODEN: JLPRAW; ISSN: 0022-2275
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The adipocyte fatty acid-binding protein, aP2 or ALBP, is an abundant cytosolic protein postulated to function in binding and intracellular transport of long-chain fatty acids. In this report, the authors investigated levels of aP2 mRNA and protein and transcriptional activity

of the aP2 gene in tissues from streptozotocin-**diabetic** rats at different time periods following the induction of **diabetes**. An av. 75% decrease in mRNA for aP2 (relative to mRNA for .beta.-actin) was obsd. in all **diabetic** rats at 7 days post-STZ injection. Insulin supplementation rapidly (2 h) restored aP2 mRNA and the insulin effect was cycloheximide-sensitive. Nuclear transcription assays measured a 60% decrease in transcription of the aP2 gene in **diabetic** rats that was reversed by insulin administration. Levels of aP2 protein were still high, in some cases, 1 day after the decrease in mRNA levels consistent with a long half-life of the protein. Decreases in aP2 protein were rapidly reversed by insulin administration. There were no changes in aP2 protein in the absence of changes in aP2 mRNA supporting a pretranslational mechanism of regulation. The decrease in aP2 mRNA was delayed in onset when compared with the rapid decline (at day 2 of **diabetes**) of mRNA for the lipogenic enzyme, fatty acid synthase, and with the accelerated depletion of adipose tissue lipid. Adipose tissue wt. and lipid content had decreased by more than 80% 3 days before any significant changes in aP2 expression were obsd. Changes in aP2 could not be related to changes in the levels of circulating fatty acids that regulate aP2 expression in vitro. The study indicated 1) that insulin deficiency and supplementation can regulate expression of aP2 in vivo and 2) that changes in aP2 levels are unlikely to contribute to the abnormalities of fatty acid metab. in adipose tissue from **diabetic** rats.

=> select hit rn l18 1;select hit rn l22 1-30;select hit rn l26 1-7;select hit rn l40 1-20;select hit rn l46 1-8

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TO SEE WHICH COMMANDS WERE EXECUTED.

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NO E#s ASSIGNED

=> select hit rn l26 1-7

NO E#s ASSIGNED

=> select hit rn l40 1-20

E1 THROUGH E1 ASSIGNED

=> select hit rn l46 1-8

NO E#s ASSIGNED

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L47 1 140602-12-6/BI
(140602-12-6/RN)

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L47 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
RN **140602-12-6** REGISTRY
CN DNA (Mus musculus clone aP2911 gene aP2 enhancer region-containing fragment) (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Deoxyribonucleic acid (Mus musculus clone aP2911 gene aP2 enhancer region-containing fragment)
OTHER NAMES:
CN 6: PN: WO0047734 SEQID: 8 unclaimed DNA
CN GenBank I16725
CN GenBank M84651
FS NUCLEIC ACID SEQUENCE
MF Unspecified
CI MAN
SR GenBank
LC STN Files: CA, CAPLUS, GENBANK, TOXLIT, USPATFULL

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2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:159935

REFERENCE 2: 124:142074